# Synopsis

## Clinical Report Synopsis for Protocol 271-15-001

**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 Comparison Trial to Assess the Efficacy and Safety of 0.3% and 1% OPA-15406 Ointments in Patients With Atopic Dermatitis

**Coordinating Investigator and Trial Centers:**

[redacted]

**Publications:** None to date.

**Trial Period:**

Date of first signed informed consent: 20 Sep 2016

Date of last trial observation: 27 Jun 2017

**Clinical Development Phase:** 2

**Trial Interruption:** There was no unplanned 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. The therapeutic strategies of AD are common in the world. 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 suppressed generally 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 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 had shown no clinically relevant safety issues and good tolerability. Also, in the phase 2 trial outside Japan, OPA-15406 1% ointment had demonstrated the efficacy on AD. Based on these results, the present trial was designed to assess the efficacy and safety of OPA-15406 ointment in Japanese AD patients.

**Objectives:**
Primary Objective:

- To evaluate Week 4 efficacy of OPA-15406 (0.3% and 1%) compared to the vehicle when administered twice daily for 8 weeks using incidence of success in Investigator's Global Assessment (IGA) as the primary endpoint in patients with AD.

Secondary Objective:

- To evaluate the safety of OPA-15406 (0.3% and 1%) when administered twice daily for 8 weeks in patients with AD.

**Methodology:**
This was a phase 2, multicenter, randomized, double-blind, vehicle-controlled, parallel-group comparison trial designed to assess the effect of OPA-15406 (0.3% and 1% random assignment) on efficacy in adult patients with AD. The trial consisted of a 2- to 30-day screening period, an 8-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 (IMP) were administered twice daily (approximately 12 hours apart between morning and night administration) for 8 weeks.

**Number of Subjects:**
Planned: Total 180 subjects
OPA-15406 0.3% group: 60 subjects
OPA-15406 1% group: 60 subjects
Vehicle group: 60 subjects

Screened: Total 223 subjects

Enrolled and treated: Total 200 subjects
OPA-15406 0.3% group: 67 subjects
OPA-15406 1% group: 67 subjects
Vehicle group: 66 subjects

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

1) Sex: Either male or female
2) Hospitalization status: Outpatient
3) Age: 15 to 70 years, inclusive (at the time of obtaining informed consent)
4) Able to provide written informed consent. For subjects under 20 years of age, written informed consent must have been obtained from both the subject and the subject's legal guardian.
5) Diagnosis of AD based on the criteria of Hanifin and Rajka
6) History of AD for at least 3 years

At screening and baseline examinations:

7) Atopic dermatitis affecting ≥ 5% to ≤ 40% of body surface area (BSA)
8) 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 OPA-15406 0.3% ointment (Lot No. 86816, expiration date: 13Nov2017) and OPA-15406 1% ointments (Lot No. 86817, expiration date: 14Nov2017).

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):**

Vehicle of OPA-15406 ointment (Lot No. 88260, expiration date: 12Nov2017)

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.

**Duration of Treatment:**

Subjects received the 0.3% or 1% formulation or the vehicle of OPA-15406 ointment twice daily (approximately 12 hours apart between morning and night administration) for 8 weeks.

**Trial Assessments:**

- *Efficacy*: IGA, eczema area and severity index (EASI), visual analogue scale (VAS) for pruritus, verbal rating scale (VRS) for pruritus, dermatology life quality index (DLQI), patient-oriented eczema measure (POEM), and affected BSA
- *Pharmacokinetics(PKs)*: Plasma concentrations and PK parameters of OPA-15406
- *Safety*: Adverse events (AEs), physical examination, vital signs (blood pressure, pulse rate, body temperature, and body weight), 12-lead electrocardiogram (ECG), and clinical laboratory tests (hematology, serum chemistry, and qualitative urinalysis)

**Criteria for Evaluation:**

*Efficacy*:

Primary Outcome Variable:

- Incidence of success in IGA at Week 4: Percentage of subjects in whom IGA score was 0 (clear) or 1 (almost clear) and improved at least 2 grades from baseline

Secondary Outcome Variables:

- Incidence of success in IGA at Week 1 and Week 8
- Change from baseline in IGA at Week 1, Week 4, and Week 8
- Change from baseline in the total score of EASI and each symptom score at Week 1, Week 4, and Week 8
- Change from baseline in VAS for pruritus at Week 1, Week 4, and Week 8
- Change from baseline in VRS for pruritus up to Day 7
- Change from baseline in the total score of DLQI at Week 1, Week 4, and Week 8
- Change from baseline in the total score of POEM at Week 1, Week 4, and Week 8
- Change from baseline in the total affected BSA (%) at Week 1, Week 4, and Week 8
- Time to response in IGA and VRS

*Pharmacokinetics*:

- Plasma trough concentrations of OPA-15406 (prior to IMP administration at Week 1, Week 4, and Week 8 of IMP administration; all subjects)
- Plasma concentrations of OPA-15406 (prior to IMP administration and 2 hours, 4 hours, and 8 hours postdose on Day 1 and at Week 4; specific trial sites; target of 6 subjects from each group)
  - Pharmacokinetic parameters of OPA-15406: $C_{max}$, $C_{max}$/Dose, $t_{max}$, $AUC_{8h}$, and $AUC_{8h}$/Dose on Day 1 and at Week 4 of IMP administration
  - Accumulation of OPA-15406: Ratio of $C_{max}$ $C_{max}$/Dose, $AUC_{8h}$, and $AUC_{8h}$/Dose at Week 4 and on Day 1 of IMP administration

*Safety*:

- Adverse events, physical examination, vital signs (including body weight), clinical laboratory values, and 12-lead ECG

**Pharmacokinetic Methods:**

*Bioanalytical*: Plasma samples were analyzed for OPA-15406 using the liquid chromatography with tandem mass spectrometry.

*Pharmacokinetics*: Non compartmental analysis was used to determine the PK parameters ($C_{max}$, $AUC_{8h}$, and $t_{max}$) for OPA-15406 on Day 1 and Week 4.

**Statistical Methods:**

*Determination of Sample Size:* In the phase 2 trial outside Japan (271-12-205), the primary variable of incidence of success in IGA had been 20.93% and 2.70% in the OPA-15406 1% group and the vehicle group, respectively. In the present trial, with the assumption that the difference in the incidence of success in IGA between the vehicle group and the OPA-15406 1% group was similar to that obtained in the foreign trial, a sample size of 54 subjects per group at a two-tailed 5% level of significance had been calculated with at least an 80% power. In consideration of possible discontinuations and dropouts, the number of subjects was established as 60 subjects per group.

*Subject Samples*:
Full Analysis Set: All subjects who received at least one dose of IMP.
Safety Set: All subjects who received at least one dose of IMP.
PK analysis set: All subjects who received at least one dose of IMP and have evaluable plasma drug concentration at least one time point.

*Efficacy*:
Primary variable was incidence of success in IGA at Week 4. The definition of the success in IGA was a subject who had an IGA score of 0 (clear) or 1 (almost clear) with an improvement by at least 2 grades from baseline (responders). The Cochran-Mantel-Haenszel test was conducted using the baseline IGA (mild or moderate) as a stratification factor. In consideration of the issue of multiplicity, the closed testing procedure was used. A comparison between the vehicle group and the OPA-15406 1% group was performed first. If there was evidence of a significant effect for OPA-15406 1% group with a two-sided significance level of 0.05, a comparison between the vehicle group and the OPA-15406 0.3% group would be performed. Also, the difference in the incidence of success in IGA and its two-sided 95% confidence interval was determined between the vehicle group and the OPA-15406 0.3% group or the OPA-15406 1% group. The 3 sensitivity analysis were conducted to confirm the primary efficacy analysis result.

*Pharmacokinetics*:
Plasma concentration of OPA-15406 as well as PK parameters of OPA-15406 were summarized by the 2 active treatment groups (0.3% and 1%) and sampling timing using descriptive statistics.

*Safety*: Adverse events were summarized in terms of number and percentage of subjects experiencing an AE. Safety variables were summarized using descriptive statistics or shift tables.

**Summary of Results:**

**Disposition, Demographics, and Baseline Characteristics:**

A total of 223 subjects were screened, from which a total of 200 were randomized and treated with IMP. Overall, 145 of 200 subjects (72.5%) completed the trial. The discontinuation rate for the OPA-15406 0.3% group, OPA-15406 1% group, and vehicle were 31.3% (21/67 subjects), 20.9% (14/67 subjects), and 30.3% (20/66 subjects), respectively. The most frequently reported reasons for discontinuation were AEs. The majority of the subjects randomized into the trial were male (130/200 subjects [65.0%]). Baseline characteristics were similar across the treatment groups.

**Efficacy Results:**

- The OPA-15406 1% group was superior to vehicle for the primary efficacy endpoint, the success rate of IGA at Week 4. The comparison had a difference of 13.22% and p-value of 0.0328. For the OPA-15406 0.3% group, the difference was 5.78% compared to the vehicle at Week 4, and although this difference was notable it was not significant (p-value = 0.3004). The success rate at Week 4 for the OPA-15406 1% group was numerically larger compared with the OPA-15406 0.3% group. The robustness of the primary analysis result was confirmed by sensitivity analyses.
- The success rates of IGA for both OPA-15406 treatment groups were numerically larger than the vehicle group at Week 4 and the following 4 weeks.
- The OPA-15406 1% group had greater least square (LS) mean decreases from baseline in IGA scores when compared to the vehicle at Weeks 1 and 4.
- Both OPA-15406 treatment groups had greater LS mean decreases from baseline in EASI scores when compared to the vehicle at Weeks 1 and 4.
- The OPA-15406 1% group had greater LS mean decreases from baseline when compared to the vehicle at Week 1 in common with the VAS score, DLQI score, POEM score, and affected BSA.
- The OPA-15406 1% group had greater LS mean decreases in VRS score at 72 hours after initiation of IMP and those decreases were continued until 168 hours.
- Notable differences were observed in EASI 50, 75, and 90 for the OPA-15406 1% group compared to the vehicle at Weeks 4 and 8 by exploratory analyses.
- These trial results suggest that OPA-15406 1% ointment is an effective treatment for AD patients.

**Pharmacokinetic Results:**

A summary of OPA-15406 PK parameters following topical application of OPA-15406 0.3% and 1% twice daily to subjects with AD are presented in the table below:

| **Mean (SD) OPA-15406 Pharmacokinetic Parameters Following Topical Application of OPA-15406 0.3% and 1% w/w Ointment Twice Daily to Subjects with Atopic Dermatitis** | | | |
|---|---|---|---|
| | **PK Parameter[a]** | **0.3% w/w (n = 11)** | **1% w/w (n = 9)** |
| Day 1 | $C_{max}$ (ng/mL) | 4.01 (5.90) | 7.27 (6.42) |

| Mean (SD) OPA-15406 Pharmacokinetic Parameters Following Topical Application of OPA-15406 0.3% and 1% w/w Ointment Twice Daily to Subjects with Atopic Dermatitis | | | |
|---|---|---|---|
| | **PK Parameter[a]** | **0.3% w/w (n = 11)** | **1% w/w (n = 9)** |
| | $C_{max}$/Dose (ng/mL/mg) | 0.269 (0.298) | 0.190 (0.146) |
| | $t_{max}$ (h)[b] | 2.05 [1.83 - 7.90] | 3.83 [1.95 - 7.87] |
| | $AUC_{8h}$ (ng·h/mL) | 22.0 (34.7) | 41.6 (37.6) |
| | $AUC_{8h}$/Dose (ng·h/mL/mg) | 1.49 (1.81) | 1.09 (0.862) |
| Week 4 | $C_{max}$ (ng/mL) | 2.07 (1.47) | 10.4 (3.68) |
| | $C_{max}$/Dose (ng/mL/mg) | 0.203 (0.132) | 0.297 (0.108) |
| | $t_{max}$ (h)[b] | 1.94 [1.83 - 8.03] | 1.84 [0.00 - 3.83] |
| | $AUC_{8h}$ (ng·h/mL) | 11.6 (7.23) | 65.2 (26.8) |
| | $AUC_{8h}$/Dose (ng·h/mL/mg) | 1.16 (0.657) | 1.86 (0.810) |

w/w = weight to weight.

[a]PK parameter were determined within the 8 hour sampling time.

[b]Median [minimum - maximum]

## Safety Results:

- There were no deaths or serious adverse events (SAEs) in this trial. A total of 37 subjects (18.5%) were discontinued from this trial due to treatment-emergent AEs (TEAEs). The number of subjects who discontinued IMP due to TEAEs by treatment group were 15 of 67 subjects (22.4%), 7 of 67 subjects (10.4%), and 15 of 66 subjects (22.7%) for the OPA-15406 0.3% group, the OPA-15406 1% group, and the vehicle, respectively.
- Treatment-emergent AEs were experienced by 78 of 200 subjects (39.0%). Treatment-emergent AEs that occurred at an incidence ≥ 5% of overall subjects were dermatitis atopic (29/200 subjects [14.5%]), viral upper respiratory tract infection (18/200 subjects [9.0%]), and pruritus (10/200 subjects [5.0%]).
- Treatment-emergent AEs considered by the investigator to be related to IMP were experienced by 20 of 200 subjects (10.0%). Dermatitis atopic (16/200 subjects [8.0%]) was the only TEAE considered by the investigator to be related to IMP that occurred at an incidence ≥ 5% of overall subjects.
- No clinically relevant trends in abnormalities were reported based on the results of clinical laboratory assessments, vital signs assessments, or ECGs.
- This trial showed that treatment with OPA-15406 (0.3% and 1%) ointment for up to 8 weeks was safe and well tolerated in subjects with AD.

## Conclusions:

- The OPA-15406 1% group was superior to vehicle for the primary efficacy endpoint, the success rate of IGA at Week 4. The success rate at Week 4 for the OPA-15406 1% group was numerically larger compared with the OPA-15406 0.3% group.

- These trial results suggest that OPA-15406 1% ointment is an effective treatment for AD patients.
- Slight accumulation of OPA-15406 PK parameters were observed upon comparison of Day 1 and Week 4, while no accumulation of OPA-15406 plasma trough concentrations was observed after 1 to 8 weeks of multiple administration.
- There were no deaths or SAEs in this trial. A total of 37 subjects were discontinued from this trial due to TEAEs.
- No clinically relevant trends in abnormalities were reported from the results of clinical laboratory assessments, vital signs assessments, or ECGs.
- This trial showed that treatment with OPA-15406 (0.3% and 1%) ointment for up to 8 weeks was safe and well tolerated in subjects with AD.

**Report Issued:** 09Jan2018