Synopsis

Clinical Report Synopsis for Protocol 271-102-00007

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 Demonstrate the Superiority of 1% OPA-15406 Ointment to the Vehicle in Adult Patients with Atopic Dermatitis (Phase 3 Trial)

Principal Investigator and Trial Centers:
This was a multicenter trial conducted at 30 sites in Japan.

Publications: None to date.

Trial Period:
Date of first signed informed consent: 25 Mar 2019

Date of last trial observation: 28 Dec 2019

Clinical Development Phase: Phase 3

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. 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 Japanease 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 efficacy and safety of OPA-15406 ointment in Japanese adult AD subjects (aged 15 to 70 years).

Objectives: The primary objective of the clinical trial was to demonstrate the superiority of 1% OPA-15406 ointment to the vehicle when administered twice-daily for 4 weeks using success rate in Investigator's Global Assessment (IGA) at Week 4 as the primary endpoint in adult subjects with AD.

The secondary objective of the clinical trial was to evaluate the efficacy (secondary endpoint) and safety of 1% OPA-15406 ointment) when administered twice-daily for 4 weeks in adult subjects with AD.

Methodology:
This was a phase 3, multicenter, randomized, double-blind, vehicle-controlled, parallel-group comparison trial designed to evaluate the efficacy and safety of OPA-15406 ointment in adult AD subjects (aged 15 to 70 years). The trial consisted of a 2- to 30-day screening period and a 4 week assessment period.

Subjects received topically the 1% formulation or the vehicle of OPA-15406 ointment. These investigational medicinal product (IMP) were administered twice-daily (approximately 12 hours apart between morning and night administration) for 4 weeks.

Number of Subjects:
Planned: Total 340 subjects
1% OPA-15406 group: 170 subjects
Vehicle group: 170 subjects

Enrolled: Total 364 subjects
1% OPA-15406 group: 182 subjects
Vehicle group: 182 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 was obtained from both the subject and the subject's legal guardian
5) Diagnosis of AD based on the Japanese Dermatological Association's criteria
6) AD affecting ≥ 5% to ≤ 40% of body surface area (BSA, excluding scalp)
7) 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 1% OPA-15406 ointment (Lot No. 109467, 109496, 109501) and vehicle of OPA-15406 ointment (Lot No. 109398, 109409, 109410). 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 1% formulation or the vehicle of OPA-15406 ointment twice-daily for 4 weeks.

Trial Assessments:
- *Efficacy*: IGA, eczema area and severity index (EASI), verbal rating scale (VRS) for pruritus, patient oriented eczema measure (POEM), Skindex-16, and affected BSA.
- *Safety*: Adverse events (AEs), clinical laboratory tests (hematology, serum chemistry, and qualitative urinalysis), physical examination, and vital signs (body temperature, blood pressure, pulse rate, and body weight).

Criteria for Evaluation:
Primary Endpoint:
- The Success rate in IGA at Week 4: percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades.

Secondary Endpoints:
- Success rate in IGA at Week 4: percentage of subjects with improved IGA score of 0 or 1 (revised definition from primary outcome variable).
- Change from baseline at Week 4 in the IGA score.
- Success rate in EASI 75 (improvement ≥ 75% in EASI), EASI 90 (improvement ≥ 90% in EASI), and EASI 50 (improvement ≥ 50% in EASI) at Week 4.
- Change from baseline at Week 4 in the total EASI score and each EASI clinical sign score.
- Change from baseline at Week 4 in VRS for pruritus.
- Change from baseline through Day 8 in VRS for pruritus.
- Change from baseline at Week 4 in the total POEM score.
- Change from baseline at Week 4 in the item score, scale score (mean score of item scores of each scale [characteristics, emotions, functions]) and mean score of the 16 items of Skindex-16.
- Change from baseline at Week 4 in the total affected BSA (%).

Safety Endpoints:

- AEs

  1) AEs occurring after the start of IMP administration (Treatment emergent adverse events [TEAEs])

  2) TEAEs by severity

  3) TEAEs resulting in death

  4) Serious TEAEs

  5) TEAEs leading to discontinuation of IMP administration

  6) TEAEs (skin and subcutaneous tissue disorders) by grade

  7) TEAEs at treatment areas

- Clinical laboratory tests
- Vital signs and body weight

Statistical Methods:

Determination of Sample Size:

In the phase 2 trial in adult patients in Japan (Trial 271-15-001), the success rate in IGA was 22.4% and 9.1% in the 1% OPA-15406 and the vehicle group, respectively. With the assumption that a similar success rate is obtained in each group, 167 subjects are necessary to achieve a power of 90% using a two-sided significance level of 5%. Therefore, the target sample size was 170 subjects in each group, a total of 340 subjects.

Subject Samples:

- Full Analysis Set (FAS): The FAS consisted of all subjects who received the IMP at least once.
- Safety Set (SS): The SS consisted of all subjects who received the IMP at least once.

Primary Endpoints:

- The success rate in IGA at Week 4 (percentage of subjects with an IGA score of 0 or 1 with an improvement of at least 2 grades).
- The efficacy of the 1% OPA-15406 group was demonstrated compared to the vehicle group based on the primary endpoint, the success rate in IGA at Week 4. For the success rate in IGA, the primary endpoint, subjects with missing IGA data was handled as non-responders. The Cochran Mantel Haenszel test was conducted at a two-sided significance level of 5% using the baseline IGA (2 or 3) as a stratification factor. The difference in the success rate in IGA and its two-sided 95% confidence interval ([CI] common risk difference adjusted by the Mantel-Haenszel method and its two-sided 95% CI) between the vehicle group and the 1% OPA-15406 group were determined. Also, the two-sided 95% CI of the success rate in IGA in the treatment group (based on Clopper-Pearson method) was calculated. Also, a supplemental analysis was performed using data which included missing data imputed by Last Observation Carried Forward (LOCF) and Observed Cases (OC) data which did not include the imputed missing data in the same manner. Week 1 and Week 2 were analyzed in the same manner as described in Week 4.

Secondary Endpoints:

- The success rate in achieving an IGA score of 0 or 1 (revised definition from primary efficacy endpoint) by Week 4 and the success rate in EASI 75, EASI 90, and EASI 50 by Week 4 were analyzed in the same manner as the primary endpoint. For IGA, subjects who achieved a score of 0 or 1 in IGA were handled as responders and subjects who did not achieve a score 0 or 1 in IGA were handled as non-responders. Subjects with missing IGA data were handled as nonresponders. EASI 75 was set as the important secondary endpoint, and subjects whose percentage change in their total EASI score from baseline decreased by ≥75% were handled as responders and subjects whose percentage change from baseline did not decrease by ≥75% were handled as nonresponders. Subjects with missing EASI 75 data were handled as nonresponders. EASI 90 and EASI 50 were analyzed in the same manner. Similarities with the primary endpoint results were assessed using response rates in EASI (EASI 75, EASI 90, and EASI 50).
- Based on the OC data set, change from baseline (Week 1, Week 2, and Week 4) in IGA scores was analyzed using a mixed model repeated measure (MMRM) with treatment (1% OPA-15406 or vehicle), time point, interaction between the treatment and time point as factors and baseline values as covariates.
- Based on the OC and LOCF data sets, shift tables were created for IGA score (0, 1, 2, 3, 4) at Week 1, Week 2, and Week 4.
- For the change from baseline in EASI, VRS, POEM, Skindex-16, and affected BSA, the analysis was performed in the same manner as for the change from baseline in IGA scores
- The success rate in IGA (IGA of 0 or 1 with improvement of at least 2 grades) and EASI 75 were analyzed for each of the following subgroups in the same manner as the primary endpoint:
  - Age: < 30 or ≥ 30 years-old
  - Sex: Male, female
  - IGA score at baseline: 2 (mild), 3 (moderate)
  - Severity of AD: mild, moderate, severe, very severe
  - Total EASI score at baseline: less than 15, 15 and above
  - Affected area at baseline: less than 20%, 20% and above

Safety Endpoints:

- All AEs were coded by system organ class and preferred term using Medical Dictionary for Regulatory Activities. Treatment emergent AEs occurring after the start of IMP administration, the number and percentage of subjects were calculated by treatment group and for all subjects. Skin and subcutaneous tissue disorders were summarized in the same manner by grade as specified in the Common Terminology Criteria for Adverse Events version 4.0 translated into Japanese by the Japan Clinical Oncology Group.
- For each clinical laboratory parameter (except qualitative urinalysis), descriptive statistics were calculated for measured values and changes from baseline at each time point by treatment group. For qualitative urinalysis values of clinical laboratory tests, a shift table at each time point against the baseline was created for each treatment group.
- For vital signs (body weight, body temperature, blood pressure [systolic and diastolic], and pulse rate), the descriptive statistics were calculated for measured values and changes from baseline at each time point by treatment group.

Summary of Results:

Disposition, Demographics, and Baseline Characteristics:

A total of 414 subjects were screened. Of those subjects, 364 were randomized and treated with IMP. Of the 364 subjects, 300 (82.4%) subjects completed and 64 (17.6%) subjects discontinued the trial. The discontinuation rates for the OPA-15406 1% group was lower than that of the vehicle group at 9.3% (17/182) subjects and 25.8% (47/182) subjects, respectively. The frequently reported reasons for discontinuation were AEs, (28/364 subjects [7.7%]), withdrawal by subject (31/364 subjects [8.5%]), and physician decision (5/364 subjects [1.4%]). Most of the reasons for discontinuation were related to AD symptoms.

The number of males (197/364 [54.1%] subjects) and females (167/364 [45.9%] subjects) were similar between the treatment groups (96/182 [52.7%] males and 86/182 [47.3%] females for the OPA-15406 1% group, and 101/182 [55.5%] males and 81/182 [44.5%] females for the vehicle group). The overall mean age was 31.9 years and was similar between the treatment groups (31.7 years for the OPA-15406 1% group and 32.1 years for the vehicle group, respectively). The majority of the subjects had IGA scores for moderate disease (311/364 [85.4%] subjects) and were similar between the treatment groups (155/182 [85.2%] subjects for the OPA-15406 1% group and 156/182 [85.7%] subjects for the vehicle group). The majority of the subjects had affected BSA $\geq$ 10% to $<$ 30% (260/364 [71.4%] subjects) and were similar between the treatment groups (135/182 [74.2%] subjects for the OPA-15406 1% group and 125/182 [68.7%] subjects for the vehicle group). The overall mean total EASI score was 10.6 and was similar between the treatment groups (10.0 for the OPA-15406 1% group and 11.3 for the vehicle group). The overall mean years since onset of AD was 24.8 years and was similar between the treatment groups (25.0 years for the OPA-15406 1% group and 24.6 years for the vehicle group).

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 25.93% and p-value of <0.0001. The robustness of the primary analysis result was confirmed by supplementary analyses.
- The OPA-15406 1% group had greater success rates in EASI 75, 90, and 50 compared to the vehicle group at Week 4. The EASI 75, 90, and 50 responder rates throughout the treatment period at Week 1 to Week 4 for the OPA-15406 1% group was larger compared to the vehicle group.
- The OPA-15406 1% group had greater decrease from baseline in EASI score, VRS score, POEM score, affected BSA, and Skindex-16 in comparison with the vehicle group over the 4 week trial.

Safety Results:

The safety variables were AEs, clinical laboratory tests, physical examinations, and vital signs.

- There was 1 SAE of dermatitis atopic that occurred after the subject completed the trial (subject was on vehicle), which resolved on 05 Oct 2019 (Day 48).
- There were no deaths reported in this trial. Twenty-eight (7.7%) subjects were discontinued from the trial due to TEAEs. The number of subjects who discontinued IMP due to TEAEs by treatment group were 3.8% (7/182 subjects) in the OPA-15406 1% group and 11.5% (21/182 subjects) in the vehicle group.
- Treatment emergent AEs were experienced by 83 of 364 subjects (22.8%) and were generally mild to moderate in severity. The incidences of TEAEs were 32 of 182 (17.6%) subjects in the OPA-15406 1% group and 51 of 182 (28.0%) subjects in the vehicle group.
- Treatment emergent AEs considered by the investigator to be related to IMP were experienced by 17 of 364 (4.7%). The incidences of IMP related TEAEs were 1 of 182 (0.5%) subjects in the OPA-15406 1% group and 16 of 182 (8.8%) subjects in the vehicle group.
- The most frequently observed TEAEs related to the IMP was dermatitis atopic (12/364 [3.3%] subjects), including 1/182 subjects (0.5%) in the OPA-15406 1% group and 11/182 subjects (6.0%) in the vehicle group.
- No clinically relevant trends in abnormalities were observed from the results of clinical laboratory and vital signs assessments.

Conclusions:

Efficacy

- The superiority of OPA-15406 1% to the vehicle was confirmed in IGA success rate at Week 4.
- Efficacy of OPA-15406 1% was also observed in other endpoints.
- OPA-15406 1% improved AD symptoms including pruritus from the first week through Week 4.
- These results suggest that OPA-15406 1% ointment is an effective treatment for adult AD in the studied population.

Safety

- No safety concerns of OPA-15406 1% group were observed.
- Treatment with OPA-15406 1% ointment BID for up to 4 weeks was safe in adult subjects with AD.