Synopsis

Clinical Report Synopsis for Protocol 271-102-00008

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 0.3% and 1% OPA-15406 Ointment to the Vehicle in Pediatric Patients with Atopic Dermatitis (Phase 3 Trial)

Principal or Coordinating 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: 07 May 2019

Date of last trial observation: 13 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 pediatric AD subjects (aged 2 to 14 years).

Objectives: The primary objective of this trial was to demonstrate the superiority of 0.3% and 1% OPA-15406 ointment to the vehicle when administered the IMP (0.3% and 1% OPA-15406 ointment or vehicle) twice daily for 4 weeks in pediatric subjects with AD, using success rate in Investigator's Global Assessment (IGA) at Week 4 as the primary endpoint.

The secondary objective of this trial was to evaluate the efficacy (secondary endpoint) and safety of 0.3% and 1% OPA-15406 ointment when administered twice-daily for 4 weeks in pediatric subjects with AD and to confirm the dose-response relationship.

Methodology:
This was a phase 3, multicenter, randomized, double-blind, vehicle-controlled, parallel-group comparison trial designed to demonstrate the superiority of 0.3% and 1% OPA-15406 ointment to the vehicle in pediatric AD subjects (aged 2 to 14 years). The trial consisted of a 2- to 30-day screening period and a 4 week assessment period.

Subjects received topically the 0.3% or 1% OPA-15406 ointment or the vehicle 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 240 subjects
0.3% OPA-15406 group: 80 subjects
1% OPA-15406 group: 80 subjects
Vehicle group: 80 subjects

Enrolled: Total 251 subjects
0.3% OPA-15406 group: 83 subjects
1% OPA-15406 group: 85 subjects
Vehicle group: 83 subjects

Diagnosis and Main Criteria for Inclusion:

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) Able to obtain written informed consent from 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) 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. 109461), 1% OPA-15406 ointment (Lot No. 109466) and vehicle of OPA-15406 ointment (Lot No. 109392). 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:
- *Efficacy*: IGA, eczema area and severity index (EASI), verbal rating scale (VRS) for pruritus (only for patients aged 7 to 14 years), patient oriented eczema measure (POEM), and affected BSA.
- *Safety*: Adverse events (AEs), clinical laboratory tests (chemistry, hematology, and urinalysis), physical examination, and vital signs (body temperature, blood pressure (systolic/diastolic), pulse rate, and body weight).

Criteria for Evaluation:
Primary Endpoint:
- 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 Eczema Area and Severity Index (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 Verbal Rating Scale (VRS) for pruritus.
- Change from baseline through Day 8 in VRS for pruritus.
- Change from baseline at Week 4 in the total Patient-Oriented Eczema Measure (POEM) score.
- Change from baseline at Week 4 in the total affected body surface area (BSA) (%).

Safety Endpoints:
- Adverse events (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:

The target sample size was set to achieve a power of 90% for the comparison of the 1% OPA-15406 group and vehicle group, which was firstly conducted in a closed testing procedure. In the phase 2 trial in pediatric patients in Japan (Trial 271-102-00002), the success rate in IGA was 37.5% (9/24), 40.0% (10/25) and 8.3% (2/24) in the 0.3% OPA-15406 group, 1% OPA-15406 group, and vehicle group, respectively. However, for reasons such as the sample size of the phase 2 trial in pediatric patients in Japan being small and in order to conservatively consider the robustness of the trial results based on the characteristics of the primary endpoint, it was assumed that if the number of responders decreased by one and increased by one in the 1% OPA-15406 group and vehicle group, respectively, then the success rate in IGA was 36% and 12%. In the case of this condition, it was necessary to have 72 subjects per group to achieve a power of 90% using a two-sided significance level of 5%. In consideration of an exploratory assessment of age categories, however, the target sample size was set as 80 subjects in each group, for a total of 240 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 improvement of at least 2 grades).
- The efficacy of the 0.3% and 1% OPA-15406 groups 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. Overall type I errors were controlled using a closed testing procedure. First, the 1% OPA-15406 treatment group and the vehicle group were compared. If significant at the two-sided significance level of 5%, the 0.3% OPA-15406 treatment group and the vehicle group were then compared at the two-

sided significance level of 5%. The Cochran-Mantel-Haenszel test was conducted for comparison using the baseline IGA (2 or 3) and age ("2 to 6 years" or "7 to 14 years") 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 0.3% or the 1% OPA-15406 group were determined. Also, the two-sided 95% CI of the success rate in IGA in each treatment group (based on Clopper-Pearson method) was calculated. In addition, the success rate in IGA in each treatment group at Week 4 and its two-sided 95% CI were plotted and the dose-response relationship was graphically assessed. A supplementary 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. Data at Weeks 1 and 2 were also analyzed in the same manner as the primary endpoint at 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 non-responders. 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 non-responders. Subjects with missing EASI 75 data were handled as non-responders. 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 (0.3% OPA-15406 or 1% OPA-15406, and vehicle), timepoint, interaction between the treatment and timepoint 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, and 4) at Weeks 1, 2, and 4.
- For the change from baseline in EASI, VRS, POEM, and affected BSA, the analysis will be 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: 2 to 6 years old, 7 years and older
  - 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 SOC and PT using MedDRA. 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 (CTCAE) 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 timepoint by treatment group. For qualitative urinalysis values of clinical laboratory tests, a shift table at each timepoint 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 timepoint by treatment group.

Summary of Results:

Disposition, Demographics, and Baseline Characteristics:

A total of 262 subjects were screened. Of those subjects, 251 were randomized and treated with IMP. Of the 251 subjects, 210 subjects (83.7%) completed and 41 subjects (16.3%) discontinued the trial. The discontinuation rates for the OPA-15406 0.3%, OPA-15406 1%, and vehicle groups were 8.4% (7/83), 10.6% (9/85), and 30.1% (25/83), respectively. The frequently reported reasons for discontinuation were withdrawal by parent/guardian (19/251 subjects [7.6%]), lack of efficacy (10/251 subjects [4.0%]), AEs (8/251 subjects [3.2%]), and withdrawal by subject (3/251 subjects [1.2%]). Most of the reasons for discontinuation were related to AD symptoms.

The number of males (135/251 subjects [53.8%]) and females (116/251 subjects [46.2%]) were similar across the treatment groups (38/83 males [45.8%] and 45/83 females [54.2%] for the OPA-15406 0.3% group, 48/85 males [56.5%] and 37/85 females [43.5%] for the OPA-15406 1% group, and 49/83 males [59.0%] and 34/83 females [41.0%] for the vehicle group, respectively). The overall mean age was 7.1 years and was similar across the treatment groups (7.1, 7.2, and 7.1 years for the OPA-15406 0.3% group, OPA-15406 1% group, and vehicle group, respectively). The majority of the subjects had IGA scores for moderate disease (212/251 subjects [84.5%]) and were similar across the treatment groups (70/83 subjects [84.3%] for the OPA-15406 0.3% group, 71/85 subjects [83.5%] for the OPA-15406 1% group, and 71/83 subjects [85.5%] for the vehicle group, respectively). The majority of the subjects had affected BSA $\geq$ 10% to < 30% (153/251 subjects [61.0%]) and were similar across the treatment groups (53/83 subjects [63.9%] for the OPA-15406 0.3% group, 54/85 subjects [63.5%] for the OPA-15406 1% group, and 46/83 subjects [55.4%] for the vehicle group, respectively). The overall mean total EASI score was 11.3 and was similar across the treatment groups (10.8, 11.6, and 11.3 for the OPA-15406 0.3% group, OPA-15406 1% group, and vehicle

group, respectively). The overall mean years since onset of AD was 5.2 years and was similar across the treatment groups (5.0, 5.1, and 5.5 years for the OPA-15406 0.3% group, OPA-15406 1% group, and vehicle group, respectively).

Efficacy Results:

- The OPA-15406 1% group was superior to vehicle for the primary efficacy endpoint, in IGA success rate at Week 4. The comparison had a difference of 28.70% and p-value of <0.0001. Similar results were observed for the OPA-15406 0.3% group, with a difference of 24.65% and p-value of 0.0005. The robustness of the primary analysis result was confirmed by supplementary analyses.
- The OPA-15406 0.3% and 1% group had greater success rates in EASI 75 compared with the vehicle group at Week4. The EASI 75, 90, and 50 responder rates at Week 4 for the OPA-15406 1% group was almost equal to or generally numerically larger compared with the OPA-15406 0.3% group.
- The OPA-15406 0.3% and OPA-15406 1% groups had greater decreases in EASI score, VRS score, POEM score, and affected BSA in comparison with the vehicle group over the 4-week trial. These efficacy parameters, except for VRS score at Week 4, for the OPA-15406 1% group were numerically larger compared with the OPA-15406 0.3% group.

Safety Results:

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

- There were no deaths or SAEs reported in subjects who were administered IMP in this trial. Eight subjects were discontinued from the trial due to TEAEs. The number of subjects who discontinued IMP due to TEAEs by treatment group were 1.2% (1/83 subjects) in the OPA-15406 0.3% group, 2.4% (2/85 subjects) in the OPA-15406 1% group, and 6.0% (5/83 subjects) in the vehicle group.
- Treatment-emergent AEs were experienced by 84 of 251 subjects (33.5%) and were generally mild to moderate in severity. The incidences of TEAEs were 32.5% (27/83 subjects) in the OPA-15406 0.3% group, 34.1% (29/85 subjects) in the OPA-15406 1% group, and 33.7% (28/83 subjects) in the vehicle group.
- Treatment-emergent AEs considered by the investigator to be related to IMP were experienced by 12 of 251 subjects (4.8%). The incidences of IMP related TEAEs were 6.0% (5/83 subjects) in the OPA-15406 0.3% group, 3.5% (3/85 subjects) in the OPA-15406 1% group, and 4.8% (4/83 subjects) in the vehicle group.
- The most frequently observed TEAEs related to the IMP was dermatitis atopic (5/251 subjects [2.0%]), including 1/83 subjects (1.2%) in the OPA-15406 0.3% group, 1/85 subjects (1.2%) in the OPA-15406 1% group, and 3/83 subjects (3.6%) in the vehicle group.
- There was no notable difference for the incidence of TEAEs between the age groups (< 7 years and age ≥ 7 years).
- 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.
- The superiority of OPA-15406 0.3% to the vehicle was also confirmed in IGA success rate at Week 4.
- Efficacy of both OPA-15406 0.3% and 1% was also observed in other endpoints.
- Both OPA-15406 0.3% and 1% improved AD symptoms including pruritus from the first week through Week4.
- These results (from Week 1 to Week 4) suggest that OPA-15406 (0.3% and 1%) ointment is an effective treatment for pediatric AD in the studied population.

Safety

- There were no differences in safety between the two OPA-15406 groups.
- No safety concerns of both OPA-15406 groups were observed.
- 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.