Protocol Synopsis

I. Protocol Title:

A Phase I/IIa Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, and Efficacy of AR100DP1 in Healthy Subjects, and Subjects with Mild to Moderate Atopic Dermatitis

II. Objectives:

Primary objective(s):

Phase I: To determine the maximum tolerated dose (MTD) of AR100DP1 in healthy subjects

Phase IIa: To assess the efficacy of AR100DP1 in treating atopic dermatitis (AD)

Secondary objective(s):

Phase I: To evaluate the safety and tolerability of AR100DP1 in healthy subjects

Phase IIa: To evaluate the safety, tolerability and efficacy of AR100DP1 in subjects with mild to moderate atopic dermatitis

III. Test Product:

1. **Name**: AR100DP1 (containing 1.25%, 2.5%, or 5% of drug substance, AR100-DS1)
2. **Dosage form**: Ointment
3. **Strength**: 20 g/tube

   0.25 g AR100-DS1/20 g (1.25%)

   0.50 g AR100-DS1/20g (2.5%)

   1.00 g AR100-DS1/20g (5%)
4. **Dosage and administration**:

   Dosage:

   1.25%, 2.5% and 5% AR100DP1

   Administration:

   In Phase I study, healthy subjects will have 14 days of treatment with AR100DP1 on the test skin area(s) of 750 cm^2 from chest and abdomen, whereas in Phase IIa study, subjects with mild to moderate AD will have 28 days of treatment with AR100DP1 on target lesion area(s). Target lesion area(s) is defined as one or multiple patches of lesion areas selected by the investigator for topical administration of AR100DP1. The size of target lesion area(s) is 0.5-5% body surface area (BSA) and the maximum is 750 cm^2 (maximal treated area, inclusive) in this study. The unit of AR100DP1 is a tube containing 20 grams (net weight) of AR100DP1 ointment. Eligible healthy subjects in Phase I will have the test skin area(s) of 750 cm^2 from chest and abdomen. For each topical administration in Phase I study, 2.5 FTUs of AR100DP1 (approximately 1,250 (± 100) mg for ~750 cm^2) will be applied to cover the test skin area(s) of eligible healthy subjects. AR100DP1 should be topically administered twice daily on the test skin area(s) of 750 cm^2 of eligible healthy subjects for 14 days in Phase I study.

Eligible subjects with mild to moderate AD in Phase IIa will have target lesion area(s) selected by the investigator.The target lesion area(s) will be selected, measured in cm^2, and recorded for AR100DP1 topical administration at Screening. The size of each patch of the target lesion area(s) will be traced, measured, and recorded at each following visit after Screening. If total lesion area of subjects is beyond 750 cm^2, other areas rather than the selected lesion areas are allowed to be treated routinely with prescribed topical medication during the study. For each topical administration in Phase IIa study, corresponding FTU(s) (approximately 1 FTU= 0.5 gram for 300 cm^2) of AR100DP1 will be applied on target lesion area(s) (0.5-5% BSA, maximum as 750 cm^2, inclusive) of eligible subjects with mild to moderate AD. AR100DP1 should be topically administered twice daily for 28 days in Phase IIa study. The skin area for AR100DP1 administration would be unchanged even when target lesion area(s) alters during the study.

5. **Mechanism of action (if known)**: Reduction of the expression of IgE, IL-17A, IL-6, IL-4, IL-1β and TNF-α. Further investigation is still ongoing.
6. **Pharmacological category**: NA

IV. Developmental phase: ■ First-in-human trial

Phase ■ I ■ II ☐ III ☐ IV ☐ Others

V. Study design:

1. ☐ Control: ☐ placebo ☐ active ☐ other
   ■ Uncontrolled
2. Blinding: ■open-label ☐evaluator blind ☐single blind ☐double blind
   ☐double dummy ☐other
3. Randomized: ☐ yes ■ no
4. ☐ Parallel ☐ Cross-over ■ Others (Phase I: 3+3 Dose escalation)
5. Duration of treatment: 14 days for Phase I, 28 days for Phase IIa
6. Titration: ☐ forced ☐ optional ■ none
7. ☐ Multi-national ■ Multi-center (Taiwan) ☐ Single center

VI. Endpoints:

1. Primary endpoint(s):

Phase I: Determine the MTD of AR100DP1

MTD is defined as the highest dose level at which < 2 of 6 subjects experienced a dose limiting toxicity (DLT) during Visit 2-6 (DLT observation period).

Phase IIa: Proportion of subjects with the Investigator's Global Assessment (IGA) score of 0 or 1 on Day 29.

2. Secondary endpoint(s):

Phase I:

Safety:

- Incidence of adverse events (AE) and serious adverse events (SAE) during Visit 2-6
- Change from baseline in vital signs at Visit 2-6
- Abnormality in physical examination at Visit 2-6
- Transition from baseline in electrocardiogram (ECG) result at Visit 3-6
- Change from baseline in laboratory parameters at Visit 3-6

Phase IIa:

Efficacy:

- Proportion of subjects achieving the Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) on Day 8, Day 15, Day 22, Day 36 and Day 43
- Change from baseline of target lesion area(s) on Day 8, Day 15, Day 22, Day 29, Day 36, and Day 43
- Change from baseline in pruritus NRS of itch level on target lesion area(s) on Day 8, Day 15, Day 22, Day 29, Day 36 and Day 43
- Change from baseline in signs of atopic dermatitis (erythema, edema/papulation, excoriation and lichenification) with grading from 0 (none) to 3 (severe) on target lesion area(s) on Day 8, Day 15, Day 22, Day 29, Day 36 and Day 43
- Change from baseline in the total score of the Patient-Oriented Eczema Measure (POEM) on Day 8, Day 15, Day 22, Day 29, Day 36 and Day 43

Safety:

- Incidence of AE and SAE during Visit 2-8
- Change from baseline in vital signs at Visit 2-8
- Abnormality in physical examination at Visit 2-8
- Transition from baseline in ECG result at Visit 3-8
- Change from baseline in laboratory parameters at Visit 3-8

Exploratory:

- Fold change of IgE on Day 15 and Day 29 compared to baseline on Day 1 (IgE_{D15}/IgE_{D1}, IgE_{D29}/IgE_{D1})
- Fold change of IL-4 on Day 15 and Day 29 compared to baseline on Day 1 ($IL\text{-}4_{D15}/IL\text{-}4_{D1}$, $IL\text{-}4_{D29}/IL\text{-}4_{D1}$)

VII. Selection criteria:

1. Main inclusion criteria

Phase I:

(1) Dated and signed informed consent
(2) Either gender, ≥ 20 years old (the legal age of consent majority is 20 years old in Taiwan)
(3) Healthy subjects, who have no clinically relevant abnormalities, identified by medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory tests
(4) Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures
(5) Healthy skin on which reddening can be easily recognized in the area of the test fields, evaluated by the investigator
(6) Subject of childbearing potential must agree to use abstinence to intercourse, or highly effective contraceptives from signing informed consent to 14 days after the last dose of study drug administration.
At least two forms of effective birth control must be adopted for contraception, and one of which must be a barrier method. Acceptable forms include:
- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom (highly recommended with spermicide), or occlusive cap (diaphragm or cervical/vault caps)

Phase IIa:
(1) Dated and signed informed consent
(2) Either gender, ≥ 20 years old (the legal age of consent majority is 20 years old in Taiwan)
(3) Confirmed clinical diagnosis of atopic dermatitis (based on the criteria of Hanifin and Rajka for AD)
(4) With at least 0.5% body surface area (BSA) as target lesion area(s)
(5) Clinical diagnosis of AD that has been clinically stable, which means the IGA score stays as 2 or 3 when evaluated for ≥ 4 weeks at the investigator's discretion prior to Screening Visit
(6) With Investigator's Global Assessment (IGA) score of 2 (mild) or 3 (moderate) at screening
(7) Subject of childbearing potential must agree to use abstinence to intercourse, or highly effective contraceptives from signing informed consent to 14 days after the last dose of study drug administration.
At least two forms of effective birth control must be adopted for contraception, and one of which must be a barrier method. Acceptable forms include:
- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom (highly recommended with spermicide),

or occlusive cap (diaphragm or cervical/vault caps)

2. Main exclusion criteria

Phase I:

(1) Subjects who have any visible skin disease at the application site which, in the opinion of the investigator, will interfere with the evaluation of the test site reaction

(2) Subjects who have a history of AD, psoriasis and/or active AD/eczema

(3) Subjects who have damaged skin in or around the test sites, including sunburn, excessively deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfigurations of the test site

(4) Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing)

Phase IIa:

(1) Unstable or actively infected AD judged by the investigator

(2) Active or potentially recurrent dermatologic condition other than atopic dermatitis that may confound evaluation (e.g. fungal infection), judged by the investigator

(3) Received systemic medication including corticosteroid, immunosuppressant, anti-histamine, phototherapy, or other therapy, which could affect AD within 4 weeks before Screening. However, subjects are allowed to enter the study if subjects have been taking at least 2 weeks of fixed dose anti-histamine prior to Screening and this application does not affect the study judged by the investigator

(4) Received topical medication including corticosteroid, immunosuppressant, anti-histamine, phototherapy, calcineurin inhibitors, or other therapy for AD on the target lesion area(s) within 1 week before Screening

The following exclusion criteria are applied for all subjects in Phase I/IIa study:

(5) Plan to receive immunosuppressive agents (including azathioprine, mycophenolate, cyclophosphamide, chlorambucil, methotrexate, cyclosporine), or systemic steroid with equivalent dosage higher than prednisolone 30 mg/day for more than 14 days at Screening

(6) Unwilling or unable to comply with the criteria in Life Style Guidelines (Section IX 1.) during the study

(7) History of use of biologic therapy (including intravenous immunoglobulin) within 12 weeks or 5 half-lives (whichever is longer)prior to Screening

(8) Received any other investigational drug within 4 weeks prior to Screening

(9) Required or received systemic CYP3A4 inhibitors with strong potency within 1 week prior to screening, including but not limited to clarithromycin, itraconazole, nefazodone and atazanavir, evaluated by the investigator

(10) Treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma, or carcinoma in situ of the skin, curatively treated with cryosurgery or surgical excision only) within 5 years before screening

(11) Had surgery within 4 weeks prior to Screening Visit, or plan to have surgery during the study

(12) Allergies requiring acute or chronic treatment at the investigator's discretion

(13) Known hypersensitivity to any of the components of the study drug

(14) Active clinically serious infection or history of human immunodeficiency virus (HIV) infection

(15) Any of the following serum test abnormalities:

- Total bilirubin > 1.5 × ULN
- AST or ALT > 3.0 × ULN
- Serum albumin < 2.5 g/dL
- Creatinine > 1.5 × ULN
- Any other ≥ Grade 2 (grading of vaccine clinical trials for Phase I and NCI-CTCAE v5.0 for Phase IIa) laboratory abnormality at baseline (other than those listed above)

(16) With ongoing acute diseases or within the past 2 years serious medical conditions (e.g. concomitant illness) such as cardiovascular (e.g. New York Heart Association (NYHA) grade III or IV), hepatic (e.g. Child-Pugh Class C), psychiatric condition (e.g. alcoholism, drug abuse), medical history, physical findings, or laboratory abnormality that in the investigators' opinion could interfere with the results of the trial or adversely affect the safety of the subject

(17) Female subject who is lactating or has positive urine pregnancy test at screening

(18) Other conditions not suitable for participating in this study judged by the investigator

VIII. Study procedures:

This Phase I/IIa study will be composed of a Phase I study in healthy subjects, and a Phase IIa study in subjects with mild to moderate atopic dermatitis. Phase I study includes 14 days of treatment with AR100DP1 on the test skin area(s) of 750 cm^2 from chest and abdomen, followed by 2 weeks of follow-up period to find the maximum tolerated dose (MTD) of AR100DP1. A single-arm Phase IIa study will be conducted with 28 days of treatment followed by 2 weeks of follow-up period to evaluate the efficacy of AR100DP1 with the recommended Phase II dose (RP2D) in treating subjects with mild to moderate atopic dermatitis (AD) on target lesion area(s). Target lesion area(s) is defined as one or multiple patches of lesion areas selected by the investigator for topical administration of AR100DP1. The size of target lesion area(s) is 0.5-5%

body surface area (BSA) and the maximum is 750 cm^2 (maximal treated area, inclusive) in this study. Eligible healthy subjects in Phase I will have the test skin area(s) of 750 cm^2 from chest and abdomen. Eligible subjects with mild to moderate AD in Phase IIa will have target lesion area(s) selected by the investigator. The skin area treated with AR100DP1 will be recorded for AR100DP1 topical administration before dosing. AR100DP1 should be topically administered twice daily on the test skin area(s) of 750 cm^2 of eligible healthy subjects for 14 days in Phase I study. The administration of AR100DP1 should be topically applied twice daily on target lesion area(s) (0.5-5% BSA, maximum as 750 cm^2, inclusive) of eligible subjects with mild to moderate AD for 28 days in Phase IIa study.

During Phase I, the study will be conducted in the conventional 3+3 design of dose escalation in three cohorts with doses as 1.25%, 2.5% and 5%, to determine the MTD of AR100DP1. The first 3 subjects of Cohort 1 (1.25%, n=3 or 6) is the sentinel group, in which subjects will be enrolled sequentially to have 7 days of AR100DP1 administration. After 7 days of dosing, the safety data will be reviewed by the investigator before the next subject of the first 3 subjects in Cohort 1 is allowed to have AR100DP1 administration. The dose of AR100DP1 will be escalated to the subsequent cohort when there is no dose-limiting toxicity (DLT) in 3 subjects or only 1 DLT in 6 subjects.

The DLT is defined as any adverse event (AE) ≥ Grade 2 (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued by United States Food and Drug Administration in September 2007), that is considered to be causally related (possibly, probably, or definitely related) to AR100DP1 as judged by the investigator during Visit 2-6 (DLT observation period). The definition of Grade 5 (death related to AE) was added to this grading system as it was not defined in the guidance. The safety results will be reviewed by the Data and Safety Monitoring Board (DSMB) after the completion of each cohort. The DSMB will provide the comments of the decision and determine if it is safe to proceed to the next dose level or stopping the dose escalation. For safety concern, the DSMB will consider to postpone the dose escalation and recruit more subjects into the concurrent dose cohort for evaluation of safety information. The DSMB will give its recommendation of the RP2D while the sponsor will determine the dosage applied in the subsequent Phase IIa study.

In the single-arm Phase IIa study, 12 evaluable subjects with mild to moderate AD are planned to be enrolled and treated with AR100DP1 at the dose determined by the sponsor for 28 days of AR100DP1 treatment period followed by a 14-day follow-up period.

1. Participating Duration

Phase I: Approximately 6 weeks, including up to 2 weeks of screening, maximal 2 weeks of treatment, and 2 weeks of follow-up.

Phase IIa: Approximately 8 weeks, including up to 2 weeks of screening, 4 weeks of treatment and 2 weeks of follow-up.

2. Study Schedule

Phase I

- **Screening (Visit 1)**

  (Day -14 - Day -1)

  - Obtain the signed informed consent form
  - Assign subject identifier number
  - Obtain demographic characteristics
  - Obtain medical history
  - Obtain medication history
  - Check eligibility
  - Perform urine pregnancy test
  - Check vital signs
  - Obtain weight and height
  - Perform physical examinations
  - Perform ECG
  - Obtain blood samples for laboratory tests
  - Record concomitant medications
  - Record adverse events

- **Treatment Period (Visit 2)**

  (Day 1)

  - Obtain vital signs (prior to and at least 30 minutes after IP administration at site)
  - Perform physical examinations (prior to and at least 30 minutes after IP administration at site)
  - Dispense diary and IP
  - Record concomitant medications
  - Record adverse events

  Before Dosing:

  - Check eligibility
  - Perform ECG
  - Recording of the test skin area(s) of 750 cm^2 from chest and abdomen

  Dosing:

  - Perform IP administration at site and record in the diary

- **Treatment Period (Visit 3)**

  (Day 8, ± 1 day)

  - Obtain vital signs
  - Perform physical examinations

- Perform ECG
- Obtain blood samples for laboratory tests
- Dispense diary and IP
- Retrieve diary and IP
- Record concomitant medications
- Record adverse events

➢ **Treatment Period (Visit 4, End of Treatment (EOT))**

(Day 15, ± 2 days)

- Perform urine pregnancy test
- Obtain vital signs
- Perform physical examinations
- Perform ECG
- Obtain blood samples for laboratory tests
- Retrieve diary and IP
- Record concomitant medications
- Record adverse events

➢ **Follow-up Period (Visit 5, Follow-up)**

(Day 22, ± 3 days)

- Obtain vital signs
- Perform physical examinations
- Perform ECG
- Obtain blood samples for laboratory tests
- Record concomitant medications
- Record adverse events

➢ **Final Visit (Visit 6)**

(Day 29, ± 3 days)

When the decision of withdrawal is made after the treatment period (Visit 4, EOT) has been completed, subjects should come back for the assessments at Final Visit within 7 days after the decision is made

- Perform urine pregnancy test
- Obtain vital signs
- Obtain weight
- Perform physical examinations
- Perform ECG
- Obtain blood samples for laboratory tests
- Record concomitant medications
- Record adverse events

- **Unscheduled Visit (UV)**

  Unscheduled visit will be arranged when investigator considered necessary or subjects have concerns. Activities to be performed will be at the investigator's discretion and will be documented in the eCRF.

  - Perform urine pregnancy test
  - Obtain vital signs
  - Perform physical examinations
  - Perform ECG
  - Obtain blood samples for laboratory tests
  - Dispense diary and IP
  - Retrieve diary and IP
  - Record concomitant medications
  - Record adverse events
  - Other activities per Investigator's decision

- **Early Termination Visit (ET)**

  ET, early termination, is defined as the decision of withdrawal is made prior to Visit 4. Subjects will be requested to complete the coming scheduled visit as ET Visit within 7 days after the last dose.

  - Perform urine pregnancy test
  - Obtain vital signs
  - Obtain weight
  - Perform physical examinations
  - Perform ECG
  - Obtain blood samples for laboratory tests
  - Retrieve diary and IP
  - Record concomitant medications
  - Record adverse events

Phase IIa

- **Screening (Visit 1)**

  (Day -14 - Day -1)

  - Obtain the signed informed consent form
  - Assign subject identifier number
  - Obtain demographic characteristics
  - Obtain medical history
  - Obtain medication history
  - Check eligibility

- Perform urine pregnancy test
- Check vital signs
- Obtain weight and height
- Perform physical examinations
- Perform ECG
- Obtain blood samples for laboratory tests
- Evaluate the IGA score of subjects with AD for eligibility
- Selection, measuring, and recording of target lesion area(s)
- Record concomitant medications
- Record adverse events

➢ **Treatment Period (Visit 2)**

(Day 1)

- Obtain vital signs (prior to and at least 30 minutes after IP administration at site)
- Perform physical examinations (prior to and at least 30 minutes after IP administration at site)
- Dispense diary and IP
- Record concomitant medications
- Record adverse events

Before Dosing:

- Check eligibility
- Perform ECG
- Evaluate the IGA score
- Self-evaluation of pruritus NRS on target lesion area(s)
- Evaluate signs of atopic dermatitis on target lesion area(s)
- Self-evaluation of POEM score
- Obtain blood sample for tests of immune response (IgE, IL-4)
- Measuring and recording of target lesion area(s)

Dosing:

- Perform IP administration at site and record in the diary

➢ **Treatment Period (Visit 3)**

(Day 8, ± 1 day)

- Obtain vital signs
- Perform physical examinations
- Perform ECG
- Obtain blood samples for laboratory tests
- Evaluate IGA score
- Self-evaluation of pruritus NRS on target lesion area(s)

- Evaluate signs of atopic dermatitis on target lesion area(s)
- Self-evaluation of POEM score
- Measuring and recording of target lesion area(s)
- Dispense diary and IP
- Retrieve diary and IP
- Record concomitant medications
- Record adverse events

➢ **Treatment Period (Visit 4)**

(Day 15, ± 2 days)

- Obtain vital signs
- Perform physical examinations
- Perform ECG
- Obtain blood samples for laboratory tests
- Evaluate IGA score
- Self-evaluation of pruritus NRS on target lesion area(s)
- Evaluate signs of atopic dermatitis on target lesion area(s)
- Self-evaluation of POEM score
- Obtain blood sample for tests of immune response (IgE, IL-4)
- Measuring and recording of target lesion area(s)
- Dispense diary and IP
- Retrieve diary and IP
- Record concomitant medications
- Record adverse events

➢ **Treatment Period (Visit 5)**

(Day 22, ± 2 days)

- Obtain vital signs
- Perform physical examinations
- Perform ECG
- Obtain blood samples for laboratory tests
- Evaluate IGA score
- Self-evaluation of pruritus NRS on target lesion area(s)
- Evaluate signs of atopic dermatitis on target lesion area(s)
- Self-evaluation of POEM score
- Measuring and recording of target lesion area(s)Dispense diary and IP
- Retrieve diary and IP
- Record concomitant medications
- Record adverse events

- **Treatment Period (Visit 6, End of Treatment (EOT))**

  (Day 29, ± 2 days)

  - Perform urine pregnancy test
  - Obtain vital signs
  - Perform physical examinations
  - Perform ECG
  - Obtain blood samples for laboratory tests
  - Evaluate IGA score
  - Self-evaluation of pruritus NRS on target lesion area(s)
  - Evaluate signs of atopic dermatitis on target lesion area(s)
  - Self-evaluation of POEM score
  - Obtain blood sample for tests of immune response (IgE, IL-4)
  - Measuring and recording of target lesion area(s)
  - Retrieve diary and IP
  - Record concomitant medications
  - Record adverse events

- **Follow-up Period (Visit 7, Follow-up)**

  (Day 36, ± 3 days)

  - Obtain vital signs
  - Perform physical examinations
  - Perform ECG
  - Obtain blood samples for laboratory tests
  - Evaluate IGA score
  - Self-evaluation of pruritus NRS on target lesion area(s)
  - Evaluate signs of atopic dermatitis on target lesion area(s)
  - Self-evaluation of POEM score
  - Measuring and recording of target lesion area(s)
  - Record concomitant medications
  - Record adverse events

- **Final Visit (Visit 8)**

  (Day 43, ± 3 days)

  When the decision of withdrawal is made after the treatment period (Visit 6, EOT) has been completed, subjects should come back for the assessments at Final Visit

  - Perform urine pregnancy test
  - Obtain vital signs
  - Obtain weight
  - Perform physical examinations

- Perform ECG
- Obtain blood samples for laboratory tests
- Evaluate IGA score
- Self-evaluation of pruritus NRS on target lesion area(s)
- Evaluate signs of atopic dermatitis on target lesion area(s)
- Self-evaluation of POEM score
- Measuring and recording of target lesion area(s)
- Record concomitant medications
- Record adverse events

➢ **Unscheduled Visit (UV)**

Unscheduled visit will be arranged when investigator considered necessary or subjects have concerns. Activities to be performed will be at the investigator's discretion and will be documented in the eCRF.

- Perform urine pregnancy test
- Obtain vital signs
- Perform physical examinations
- Perform ECG
- Obtain blood samples for laboratory tests
- Evaluate IGA score
- Self-evaluation of pruritus NRS on target lesion area(s)
- Evaluate signs of atopic dermatitis on target lesion area(s)
- Self-evaluation of POEM score
- Obtain blood sample for tests of immune response (IgE, IL-4)
- Measuring and recording of target lesion area(s)
- Dispense diary and IP
- Retrieve diary and IP
- Record concomitant medications
- Record adverse events
- Other activities per Investigator's decision

➢ **Early Termination Visit (ET)**

ET, early termination, is defined as the decision of withdrawal is made prior to Visit 6. Subjects will be requested to complete the coming scheduled visit as ET Visit within 7 days after the last dose.

- Perform urine pregnancy test
- Obtain vital signs
- Obtain weight
- Perform physical examinations

- Perform ECG
- Obtain blood samples for laboratory tests
- Evaluate IGA score
- Self-evaluation of pruritus NRS on target lesion area(s)
- Evaluate signs of atopic dermatitis on target lesion area(s)
- Self-evaluation of POEM score
- Obtain blood sample for tests of immune response (IgE, IL-4)
- Measuring and recording of target lesion area(s)
- Retrieve diary and IP
- Record concomitant medications
- Record adverse events
- Other activities per Investigator's decision

3. Study Intervention Discontinuation and Subject Withdrawal for Discontinuation

3.1 Study Intervention Discontinuation

When the discontinuation is confirmed, subjects will be requested to complete the coming scheduled visit as early termination (ET) Visit within 7 days after the last dose. When the decision of withdrawal is made at the scheduled visit prior to the end of treatment (EOT), that same visit will be deemed as ET Visit, which means the assessments scheduled for ET will be evaluated. When the decision of withdrawal is made at an Unscheduled Visit, the same Unscheduled Visit will be deemed as ET Visit and the assessments at this visit will follow those defined at ET visit. When the decision of withdrawal is made after the treatment period (EOT) has been completed, subjects are requested to return for assessments scheduled at Final Visit within 7 days after the decision is made. AEs will be followed up until resolved or stable. Alternatively, if the subject does not agree to this option or is not able to physically attend the visit, a modified follow up by telephone contact should be arranged, if agreed to by the subject and in compliance with local data privacy laws/practices.

3.2 Subject Withdrawal from the study

Subjects are free to withdraw from participation in the study at any time and for any reason, or no reason at all upon request, without prejudice.

An investigator may discontinue or withdraw a subject from the study for the following reasons:

1. Any pathological event, clinical adverse event, laboratory abnormality, intercurrent illness, or any occurrence or change in the subject's physically and/or psychologically status giving indication to the investigator that further participation in the study may not be the best interest of the subject.
2. Subject develops DLT during the study period. (Phase I only)

3. Subject develops disease progression judged by the investigator. (Phase IIa only)
4. The subject's pregnancy from Screening Visit until Final Visit. Subject's pregnancy status should be checked by urine pregnancy test according to the SOA or if investigator or subject suspects the subject is pregnant.
5. The subject was enrolled by error and/or it is discovered that the subject does not meet the eligibility criteria after enrollment.
6. The subject does not take, or is unable to take, the study medication as instructed, does not keep appointments, or otherwise does not adhere to protocol requirements.
7. The subject dies or is lost to follow-up.
8. The study is terminated prematurely by the investigator, research institution, sponsor, IRB/IEC or regulatory authorities.
9. Subject does not receive medical benefit as considered by the investigator

IX. Concomitant treatment:

1. Permitted

Life Style Guidance

During this study:

1. Subjects will be advised to abstain from consumption of alcohol during the study.
2. Subjects will be advised to abstain from consumption food containing CYP3A4 inhibitors, as red wine, grapefruit or grapefruit-related citrus fruits (e.g., Seville oranges, pomelos) during the study.
3. Subjects should keep target lesion area(s) or the test skin area(s) clean and dry, avoiding from covering target lesion area(s) or the test skin area(s) with next-to-skin clothes as well as applying reagents other than AR100DP1 topical administration to target lesion area(s) or the test skin area(s).
4. Subjects should avoid from strenuous exercise (e.g., heavy lifting, weight training, calisthenics, aerobics) during the study.
5. Subjects should avoid from water recreation, which is potentially related to water immersion (e.g., swimming, SPA (salus per aqua), hot spring baths, water rafting) during the study.

2. Prohibited

The following medications are prohibited until Final Visit:

- **Phase IIa only**: Systemic medication including corticosteroid, immunosuppressant, anti-histamine, phototherapy, or other therapy, which could affect AD within 4 weeks prior to Screening Visit until Final Visit. However, subjects, who have been taking at least 2 weeks of fixed dose anti-histamine prior to Screening and this application does

not affect the study judged by the investigator, are exceptions

- **Phase IIa only**: Topical medication including corticosteroid, immunosuppressant, anti-histamine, phototherapy, calcineurin inhibitors, or other therapy for AD on the target lesion area(s) within 1 week prior to Screening Visit until Final Visit
- Immunosuppressive agents (including azathioprine, mycophenolate, cyclophosphamide, chlorambucil, methotrexate, cyclosporine), or systemic steroid with equivalent dosage higher than prednisolone 30 mg/day for more than 14 days from Screening Visit until Final Visit
- Biologic therapy (including intravenous immunoglobulin) within 12 weeks or 5 half-lives (whichever is longer) prior to Screening until Final Visit
- Any other investigational drug within 4 weeks prior to Screening until Final Visit
- Systemic CYP3A4 inhibitors with strong potency within 1 week prior to Screening Visit, including but not limited to clarithromycin, itraconazole, nefazodone and atazanavir, evaluated by the investigator until Final Visit
- Treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma, or carcinoma in situ of the skin, curatively treated with cryosurgery or surgical excision only) within 5 years prior to Screening Visit until Final Visit
- Surgery within 4 weeks prior to Screening Visit until Final Visit

X. Statistics:

1. **Primary hypothesis**: ☐ superiority ☐ non- inferiority ☐ equivalence ■ other
2. **Sample size**: Enrolled 35 subjects (Phase I: 21 subjects/Phase IIa: 14 subjects)
   Evaluable 30 subjects (Phase I: 18 subjects/Phase IIa: 12 subjects)
3. **Efficacy population**: ■ ITT ■ PP (Phase IIa only) ■ Other (PP-EOT, Phase IIa only)
   Safety population: ■ ITT ☐ PP ■ Other (MTD, Phase I only)

Intent-to-treat (ITT) population:

- Enrolled subjects receiving at least one dose of AR100DP1

MTD population (Phase I Only):

- Eligible subjects who administered at least one dose of the investigational product and experienced DLT
  OR
- Eligible subjects who were dosed for at least 12 days with at least 85% of compliance.

Per-protocol before End of Treatment (PP-EOT) population (Phase IIa Only):

- A subset of ITT population
- Fulfill all inclusion and exclusion criteria
- Subjects dosed for at least 21 days of Phase IIa with at least 75% of compliance
- No major protocol deviation which could affect the efficacy assessment

- Not take any prohibited therapy before End of Treatment (EOT) Visit assessment

Per-protocol (PP) population (Phase IIa Only):

- A subset of PP-EOT population
- Not take any prohibited therapy during the study

Efficacy analysis will be conducted in ITT, PP-EOT and PP population for Phase IIa study. Demographic, baseline characteristics and safety analyses will be conducted in ITT population for both Phase I and Phase IIa studies. Efficacy results for Phase IIa study will be concluded in ITT population.

4. Statistical method(s) for efficacy/safety evaluations:

General Approach

Descriptive statistics will be provided for all endpoints by dose level (dose level of Phase I, and RP2D of Phase IIa).

Continuous variables will be summarized by reporting the number of observations, mean, standard deviation, median, interquartile range (IQR = third quartile (Q3) - first quartile(Q1)), Q1, Q3, minimum and maximum.

Categorical variables will be summarized by using frequency tables showing the number and percentage of subjects within a particular category.

Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint of the Phase I study is to determine MTD of AR100DP1 in healthy subjects, which is a safety endpoint. Such endpoint will be observed on evaluable subjects. While in the Phase IIa study, the primary endpoint is the proportion of subjects with the IGA score of 0 or 1 (responder) on Day 29. Frequency tables of response rate and change from baseline of IGA score will be presented respectively The last-observation-carried-forward (LOCF) method will be applied if all subsequent visits are missing.

Analysis of the Secondary Endpoint(s)

Efficacy Endpoints:

For Proportion of subjects with the IGA score of 0 or 1.

Change from baseline of target lesion area(s), change from baseline in pruritus NRS of itch level on target lesion area(s), change from baseline in signs of atopic dermatitis (erythema, edema/papulation, excoriation and lichenification) on target lesion area(s), and change from baseline in the total score of the POEM will be analyzed by using descriptive statistics, p-value of Wilcoxon sign-rank test or paired-t test will be given to test the improvement. Frequency tables of change from baseline will be presented for pruritus NRS of itch level, and

the total score of the POEM as appropriate.

Safety Analyses

Adverse events will be coded by employing Medical Dictionary for Regulatory Activities (MedDRA). The version of MedDRA used for coding should be agreed by sponsor before coding starts. AE will be displayed by subject count, i.e. each subject is counted only once within each category of AE. The incidence of AEs will be presented by System Organ Class (SOC) and preferred term groupings. For Phase I, incidence of DLT will be presented on both ITT population and evaluable subjects. The information of AEs, such as start date, stop date, severity, relationship, expectedness (only for SAE), outcome, and duration, should be listed. Adverse events leading to premature discontinuation from the study intervention and serious adverse events (SAEs) should be presented either in a table or a listing.

Findings in physical examinations will be displayed for each individual system. Findings in ECG will be tabulated with transition from baseline. Net changes from baseline laboratory parameters, weight and vital signs will be analyzed by using descriptive statistics with p-value of Wilcoxon sign-rank test or paired-*t* test given. The baseline is defined as the closest test result prior to the first dosing of AR100DP1 topical administration.

5. Planned interim analysis: ■ yes ☐ no
Interim analysis will be performed upon the completion of Phase I study.

XI. Please attach flow chart and/or assessment schedule, if available:

Phase I

Procedures/Assessments	Screening	Study Period					Unscheduled	
		Treatment			Follow-up	Final[m]		
Visit	**1**	**2[f]**	**3***	**4 EOT[k]**	**5**	**6**	**Early Termination (ET[l]) Visit**	**Unscheduled Visit (UV) during Study Period[a]**
Day	**-14 - -1**	**1**	**8**	**15**	**22**	**29**		
Window period (days)	**-**	**-**	**± 1**	**± 2**	**± 3**	**± 3**		
Informed consent	X							
Identifier number	X							
Demographics	X							
Medical history	X							
Medication history	X							
Eligibility	X	X[g]						
Pregnancy test[b]	X			X		X	X	X
Vital signs	X	X[g,h]	X	X	X	X	X	X
Weight & height[i]	X					X	X	

Physical examination	X	X[g,h]	X	X	X	X	X	X
ECG[c]	X	X[g]	X	X	X	X	X	X
Laboratory test[d,e]	X		X	X	X	X	X	X
Recording of the test skin area(s)[g]		X						
IP administration at site		X[h]						
Dispense diary and IP[j]		X	X					X
Retrieve diary and IP[j]			X	X			X	X
Concomitant medications	X	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X	X

Note:

* On the days of scheduled visits, subjects are advised to have NO IP administration prior to completion of scheduled assessments.

a. Unscheduled visits and actions at the visit will be arranged at the investigator's discretion.
b. Pregnancy tests performed within 2 days before each designated visit will be acceptable.
c. ECG tests performed within the window period and prior to each designated visit (Visit 3-6) will be acceptable.
d. Laboratory tests performed within 7 days before Screening Visit and within 2 days before other visits will be acceptable.
e. Laboratory tests include hematology (hemoglobin, hematocrit, RBC, platelet, WBC with differential counts) and biochemistry (total bilirubin, AST, ALT, serum creatinine, albumin).
f. The eligibility check at Visit 2 will be based on the results of pre-treatment measurements scheduled at Visit 2, accompanying with other information obtained at Visit 1 before IP administration at the study site.
g. Procedures to be performed before IP administration.
h. Subjects will be observed for at least 30 minutes for vital signs and physical exam again after AR100DP1 topical administration at the study site. IP will be applied for twice on Day 1 regardless if the visit is at AM or PM.
i. The height is only measured at Screening Visit.
j. The weight of IP will be recorded when dispensing and returning. Actions scheduled on unscheduled visit are optional.
k. EOT, end of treatment, means the visit right after the treatment period is completed.
l. ET, early termination, is defined as the decision of withdrawal is made prior to Visit 4. Subjects will be requested to complete the coming scheduled visit as ET Visit within 7 days after the last dose.
m. When the decision of withdrawal is made after the treatment period (Visit 4, EOT) has been completed, subjects should come back for the assessments at Final Visit within 7 days after the decision is made.

Phase IIa

Procedures/ Assessments	**Screening**	**Study Period**							**Unscheduled**	
		Treatment					**Follow-up**	**Final[m]**		
Visit	**1**	**2[f]**	**3***	**4***	**5***	**6 EOT[k]**	**7**	**8**	**Early Termination (ET[l]) Visit**	**Unscheduled Visit (UV) during Study Period[a]**
Day	**-14 ~ -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**		
Window period (days)	**-**	**-**	**± 1**	**± 2**	**± 2**	**± 2**	**± 3**	**± 3**		
Informed consent	X									
Identifier number	X									
Demographics	X									
Medical history	X									
Medication history	X									
Eligibility	X	X[g]								
Pregnancy test[b]	X					X		X	X	X

Vital signs	X	X[g,h]	X	X	X	X	X	X	X	X
Weight & height[i]	X							X	X	
Physical examination	X	X[g,h]	X	X	X	X	X	X	X	X
ECG[c]	X	X[g]	X	X	X	X	X	X	X	X
Laboratory test[d,e]	X		X	X	X	X	X	X	X	X
IGA score	X	X[g]	X	X	X	X	X	X	X	X
Pruritus NRS on target lesion area(s)		X[g]	X	X	X	X	X	X	X	X
Signs of atopic dermatitis on target lesion area(s)		X[g]	X	X	X	X	X	X	X	X
POEM score		X[g]	X	X	X	X	X	X	X	X
Immune response (IgE, IL-4)		X[g]		X		X			X	X
Selection, measuring, and recording of target lesion area(s)[n]	X	X[g]	X	X	X	X	X	X	X	X
IP administration at site		X[h]								
Dispense diary and IP[j]		X	X	X	X					X
Retrieve diary and IP[j]			X	X	X	X			X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X	X	X	X

Note:

* On the days of scheduled visits, subjects are advised to have NO IP administration prior to completion of scheduled assessments.

a. Unscheduled visits and actions at the visit will be arranged at the investigator's discretion.

b. Pregnancy tests performed within 2 days before each designated visit will be acceptable.

c. ECG tests performed within the window period and prior to each designated visit (Visit 3-8) will be acceptable.

d. Laboratory tests performed within 7 days before Screening Visit and within 2 days before other visits will be acceptable.

e. Laboratory tests include hematology (hemoglobin, hematocrit, RBC, platelet, WBC with differential counts) and biochemistry (total bilirubin, AST, ALT, serum creatinine, albumin).

f. The eligibility check at Visit 2 will be based on the results of pre-treatment measurements scheduled at Visit 2, accompanying with other information obtained at Visit 1 before IP administration at the study site.

g. Procedures to be performed before IP administration.

h. Subjects will be observed for at least 30 minutes for vital signs and physical exam again after IP administration at the study site. IP will be applied for twice on Day 1 regardless if the visit is at AM or PM.

i. The height is only measured at Screening Visit.

j. The weight of IP will be recorded when dispensing and returning. Actions on unscheduled visit are optional.

k. EOT, end of treatment, means the visit right after the treatment period is completed.

l. ET, early termination, is defined as the decision of withdrawal is made prior to Visit 6. Subjects will be requested to complete the coming scheduled visit as ET Visit within 7 days after the last dose.

m. When the decision of withdrawal is made after the treatment period (Visit 6, EOT) has been completed, subjects should come back for the assessments at Final Visit within 7 days after the decision is made.

n. Selection is only executed at Screening. Measuring and recording are executed at every visit.