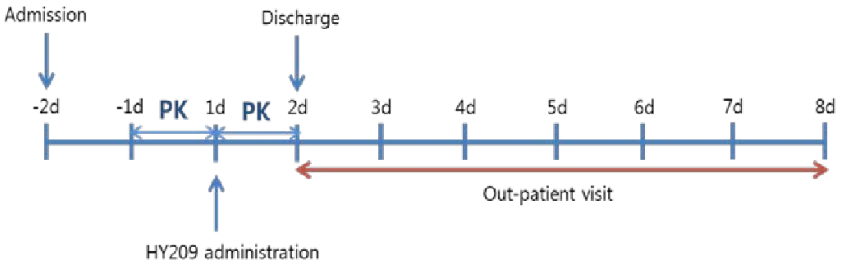
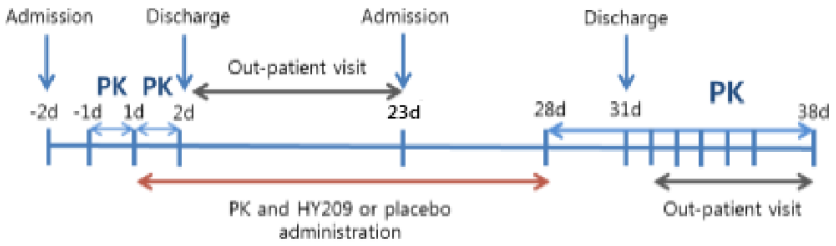
A randomized, double-blind, placebo-controlled single and multiple dosing, escalation phase I clinical trial to investigate the safety/tolerability and pharmacokinetics of HY209 gel after transdermal administration in healthy male volunteers

Protocol No.	HY209-AD (version 1.5 Date: 2019.01.20)
National Clinical Trial No.	NCT03492398
Investigational Product	HY209 0.05%, 0.1%, 0.3%, 0.5%
Development phase of study	Phase I
Institutes	Seoul National University Hospital
Sponsor	Shaperon, Inc.

▣ AD Phase I Synopsis

Study Title	A randomized, double-blind, placebo-controlled single and multiple dosing, dose escalation phase I clinical trial to investigate the safety/tolerability and pharmacokinetics of HY209 gel after transdermal administration in healthy male volunteers
Sponsor	Shaperon, Inc.
Institutes	Seoul National University Hospital.
Target disease	Atopic Dermatitis
Purpose	The purpose of this study is to evaluate the safety, tolerability and pharmacokinetics of HY209 gel as a possible treatment option for atopic dermatitis.
Study Design	Randomized, double-blind, placebo-controlled (single and multiple dosing), dose escalation phase I clinical trial
Study Method	(1) Cohort A Single dosing Four groups (HY209 0.05%, 0.1%, 0.3%, 0.5%) of subjects, each group consisting of control 6 and placebo 2 will be randomly selected. The trial drug or placebo will be applied on the back of each subject. Subjects will be released after present tests and blood drawing.  (2) Cohort B Multiple dosing Three groups (HY209 0.05%, 0.1%, 0.3%) of subjects, each group consisting of control 6 and placebo 2 will be randomly selected. The trial drug or placebo will be applied on the back of each subject at once a day for 28 days. Subjects will visit the clinical research center to be tested and have their blood drawn,

▣ AD Phase I Synopsis

<table>
<tr><td></td><td> 
</td></tr>
<tr><td>Investigational Product</td><td>• Investigational Product: HY209 0.05%, 0.1%, 0.3%, 0.5%
• Control Product: Placebo (Vehicle)</td></tr>
<tr><td>Treatment</td><td>(1) Cohort A Single dosing
• Once at Day 1
(2) Cohort B Multiple dosing
• Once daily for 28 days</td></tr>
<tr><td>Estimated Subjects</td><td>(1) Cohort A Single dosing (total 32 subjects)
<table>
<tr><th>Group</th><th>Dose</th><th>Number of subjects</th></tr>
<tr><td>1</td><td>HY209 0.05%</td><td>8 (HY209; 6, placebo; 2)</td></tr>
<tr><td>2</td><td>HY209 0.1%</td><td>8 (HY209; 6, placebo; 2)</td></tr>
<tr><td>3</td><td>HY209 0.3%</td><td>8 (HY209; 6, placebo; 2)</td></tr>
<tr><td>4</td><td>HY209 0.5%</td><td>8 (HY209; 6, placebo; 2)</td></tr>
</table>
(2) Cohort B Multiple dosing (total 24 subjects)
<table>
<tr><th>Group</th><th>Dose</th><th>Number of subjects</th></tr>
<tr><td>5</td><td>HY209 0.05%</td><td>8 (HY209; 6, placebo; 2)</td></tr>
<tr><td>6</td><td>HY209 0.1%</td><td>8 (HY209; 6, placebo; 2)</td></tr>
<tr><td>7</td><td>HY209 0.3%</td><td>8 (HY209; 6, placebo; 2)</td></tr>
</table>
The objective of this study is an exploratory study to evaluate the safety, tolerability, and pharmacokinetics of HY209, the number of subjects was not determined based on statistical considerations.</td></tr>
<tr><td>Inclusion Criteria</td><td>1) Healthy male aged from 20 to 50
2) Weight minimum 45 kg, maximum 90 kg with BMI minimum 17 kg/m^2 maximum 27 kg/m^2
➢ BMI (kg/m2) = weight (kg) / [height (m)]^2</td></tr>
</table>

▣ AD Phase I Synopsis

	3) No skin diseases, no skin damages (scars, tattoo, etc.), no hairy skin in drug-applied area which may cause the alteration of drug absorption 4) Those who must be capable of giving informed consent and willing to comply with all clinic visits and study-related procedures until study completion
Exclusion Criteria	1) Those who have a history of hypersensitivity or clinically significant hypersensitivity reactions to drugs (containing Taurodeoxycholate component, aspirin, antibiotics, etc.) 2) Those who have clinically significant liver, kidney, respiratory, endocrine, neurologic diseases or hematologic diseases, mental diseases, especially hemorrhagic diseases (hemophilia, von Willebrand disease, etc.), cardiovascular diseases (coronary artery diseases, congestive heart failure, arrhythmia, cerebrovascular diseases, etc.) or who have a history of those diseases 3) Those who have clinical symptoms suspected of acute infectious disease within 2 weeks before the schedule date of the first administration, or whose temperature measured by the screening test was 38℃ or higher 4) Those who have taken any ETC medicines, herbal medicines, crude drugs within 2 weeks before the scheduled date of administration of medicines for clinical trials, or OTC medicines or vitamin preparations within 1 week (if all other selection / exclusion criteria are met. The researcher should consult with the sponsor to determine whether it is appropriate to take the subject into the trials, considering the safety of the subject or the effect on overall clinical trial results.) 5) Those who have a history of substance abuse, or positive urine screening tests (cannabinoid, opiates, amphetamine, cocaine, barbiturate, benzodiazepine) 6) Those who have a history of smoking within 3 months (However, if they quit smoking three months before the first scheduled medication, they are eligible for selection) 7) Those who have been found to be positive in serological tests (HBs

▣ AD Phase I Synopsis

	antigen, HCV antibody and HIV antibody) 8) Those who drink continuously (above 21 units / week, 1 unit = 10 g of pure alcohol) 9) Those who have been taking medicines by participating in other clinical trials or bioequivalence studies within 3 months prior to the date of first dosing (the time from the date of the previous clinical trial will be based on the date of administration of each relevant clinical trial drug, If the half-life of a test drug taken in a clinical trial is more than two weeks, it may be attained more than five times the expected half-life of the test drug.) 10) Those who have been bleeding, blood drawings or blood donation of 400mL or more within 8 weeks before the scheduled date of administration of the drug for clinical trials 11) Those who have vital signs measured at sitting postion after the break for more than 3 minutes, ➢ Low blood pressure (systolic blood pressure < 90 mmHg, diastolic blood pressure < 50 mmHg) ➢ High blood pressure (systolic blood pressure greater than 150 mmHg, diastolic blood pressure greater than 100 mmHg) 12) Test subjects who are deemed unsuitable for participating in clinical trials due to clinical laboratory tests, ECG results, or other reasons
Outcome Measures	• **Primary Outcome Measures** 1) Safety and tolerability assessment ➢ Adverse events, physical symptoms, vital signs, physical test, electrocardiography, clinical laboratory test, local stimulation assessment, numerical plan rating scale • **Secondary Outcome Measures** 1) Pharmacokinetics ➢ $C_{max, ss}$, $C_{min, ss}$, $AUC_{inf, T, ss}$, $T_{max, ss}$, $t_{1/2, ss}$, CL/F