STUDY PROTOCOL

Protocol Title	**Efficacy and Safety of Enstilar Foam in Combination with Apremilast (Otezla) in Patients with Moderate Plaque Psoriasis**
Protocol Date	**July 6, 2017**
Protocol number:	**ENS-1701**
Investigator/Sponsor	**Leon Kircik, MD** **Skin Sciences, PLLC** **1169 Eastern Parkway, Suite 2310** **Louisville, KY 40217**

PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the supplements, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality. This study will be conducted per protocol according to local legal and regulatory requirements, and in accord with the spirit of GCP. However, will not adhere to the requirements of the comprehensive ICH-GCP guidelines.

Investigator

Printed Name	Signature	Date

STUDY OBJECTIVE

The combination treatment of topicals and systemic medications in psoriasis has been traditionally used by community dermatologists. However, there is no significant data from clinical studies to reveal the additional benefit of the combination since all registration studies have to be done as monotherapy. It will be very usfull data for practicing dermatologist to show the additional benefit of Enstilar with Otezla in moderate plaque type psoriasis patients.

1.1 Primary Endpoint

Percent of subjects with PASI 75 at week 16 in Enstilar plus Otezla group versus vehicle plus Otezla group.

Secondary Endpoints: PASI 75 at week 4 and at week 12.
PASI 90 and 100 at week 16.
PGA at week 4 and week 12 and week 16.
Itch VAS at week 4, 12, and 16. DLQI at week 4, 12 and 16.

2 STUDY DESIGN

This is a four-center, investigator-blind study. Approximately 50 qualified subjects will be enrolled into a 16 weeks study. Subjects will be randomized to study treatment at a 1:1 ratio: of Otezla plus Enstilar foam versus Otezla plus vehicle foam. All adverse events and con meds will be recorded throughout the study.

Group A *n = 25*	Otezla plus Enstilar Foam
Group B *n = 25*	Otezla plus Vehicle Foam

Subjects will attend a Screening Visit/Baseline visit and if found eligible will be randomized to study treatment. Patients will be counselled on the use of the study medication and the medications will be labelled for the appropriate group as noted above. Subjects with moderate plaque type psoriasis who have been started on commercial Otezla within the last 7 days will be randomized either to Enstilar Foam or vehicle foam for the first 4 weeks.

Enstilar or the vehicle will be initiated for the first 4 weeks and then Otezla will be continued as monotherapy for the next 8 weeks and then Enstilar or the vehicle will be re-initiated for the last 4 weeks of the study. Total study period is 16 weeks. Study visits will be, screening/baseline, week 1, 2, 3, 4, , week 12, and week 16. Study assessments will be at each visit: PASI, BSA, PGA, Itch VAS, DLQI, in addition to standard medical assessments. There will be a standard prohibited medcation/treatment and washout periods.

3 SELECTION AND WITHDRAWAL OF SUBJECTS

3.1 Inclusion Criteria

i. Outpatient, male or female subjects of any race, 18 years of age or higher. Female subjects of childbearing potential must have a (-)UPT result at within 7 days of the first dose of study drug and practice a reliable method of contraception throughout the study;

A female is considered of childbearing potential unless she is:

- *postmenopausal ≥ 5Y, without a uterus and/or both ovaries; or has been surgically sterile for ≥ 6M.*

Reliable methods of contraception are:

- *hormonal methods or IUD in use ≥ 90d prior to study drug administration, barrier methods plus spermicide in use ≥ 14d prior, or vasectomized partner.*

[Exception: Female subjects of CBP who are not sexually active are not required to practice a reliable method of contraception and may be enrolled at the Investigator's discretion provided they are counseled to remain sexually inactive for the duration of the study and understand the risks involved in getting pregnant during the study.]

ii. Subjects with moderate plaque type psoriasis who have been started on commercial Otezla within the last 10 days.

iii. Physician Global Assessment (PGA) score of 3.

iv. Able to understand study requirements and sign Informed Consent/HIPAA forms.

3.2 Exclusion Criteria

i. Female subjects who are pregnant, breast-feeding, or who are of childbearing potential and not practicing a reliable method of birth control, or male subjects planning a pregnancy with their spouse or partner while in the study.

ii. History of hypercalcemia or vitamin D toxicity or history of significant renal or hepatic disease

iii. Patients with guttate, erythrodermic, or pustular psoriasis

iv. Serious skin condition (other than psoriasis) or uncontrolled medical condition (in the opinion of the investigator).

v. Skin conditions (e.g. eczema) psoriasis that may interfere with evaluations of psoriasis.

vi. Known hypersensitivity to Enstilar Foam or any of its components.

vii. Current drug or alcohol abuse (Investigator opinion).

viii. Subject unable to commit to all the assessments required by the protocol.

ix. Current enrollment in another clinical study and treatment with another experimental drug or approved therapy for experimental use within 30 days prior to the Screening Visit.

3.3 Withdrawal of Subjects

It is the right and duty of the Investigator to discontinue the study participation of a subject when the subject's health or well-being is threatened by continuation in the study. Such subjects should be withdrawn from the study and not continued under a modified regimen. The following are circumstances that would result in the subject's discontinuation from the study:

- the subject experiences a serious adverse event rendering them unable to continue study participation;
- the subject is unable to physically or mentally tolerate the use of the test medication;
- an exclusion criterion becomes apparent at any time during the study; or
- the subject voluntarily withdraws.

In the event of premature discontinuation from the study, the Investigator should determine the primary reason for discontinuation.

If a subject withdraws for any reason, the subject will be replaced.

4 TREATMENT OF SUBJECTS AND FOLLOW-UP

4.1 Study Procedures

4.1.1 Assessment Schedule

Assessment	Screening -30days to -1 days	Baseline DAY 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 12	Wk 16
Written informed consent	X							
Medical history	X	X						
demographics	X							
Physical exam	X	X	X	X	X	X	X	X
Prior Disease therapies	X							
Vital signs with Weight	X	X	X	X	X	X	X	X
Height	X	X						
Urine pregnancy	X	X	X	X	X	X	X	X
Review inclusion/exclusion	X	X						
%BSA	X	X	X	X	X	X	X	X
Investigator Global Assessment (IGA)	X	X	X	X	X	X	X	X
PASI	X	X	X	X	X	X	X	X
Patient Satisfaction Survey	X	X				X	X	X
Subject assessment of pruritus VAS	X	X	X	X	X	X	X	X
DLQI	X	X				X	X	X
Study drug – D – dispense C – collect		D	C D	C D	C D	C	D	C
Adverse events	X	X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X
Prior and concomitant procedures	X	X	X	X	X	X	X	X

4.1.2 Screening Visit/ Baseline Visit

- Informed Consent/HIPAA
- Urine Pregnancy Test *(if applicable)*
- Subject Demographics/Medical History
- Concomitant Medication/Treatment
- Inclusion/Exclusion Criteria
- Assessments
  - *BSA (Affected Body Surface Area)*
  - *PGA*
  - *PASI*

- Physical Exam
- Vital Signs with weight/height
- Patient satisfaction survey
- Subject assessment of pruritus VAS
- DLQI
- Drug dispensation
- Prior disease therapies
- Adverse events

4.1.3 Week 1

- Urine Pregnancy Test *(if applicable)*
- Vital signs with weight
- Concomitant Medication/Treatment
- Physical Exam
- Subject assessment of pruritus VAS
- Drug dispensation / collectionAdverse Events
- Collect & Weigh study drug
- Assessments
  - *BSA (Affected Body Surface Area)*
  - *PGA*
  - *PASI*

Week 2

- Urine Pregnancy Test *(if applicable)*
- Vital signs with weight
- Concomitant Medication/Treatment
- Physical ExaSubject assessment of pruritus VAS
- Drug dispensation / collection
- Adverse Events
- Collect & Weigh study drug
- Assessments
  - *BSA (Affected Body Surface Area)*
  - *PGA*
  - *PASI*

Week 3

- Urine Pregnancy Test *(if applicable)*
- Vital signs with weight
- Concomitant Medication/Treatment
- Physical Exam
- Subject assessment of pruritus VAS
- Drug dispensation / collection
- Adverse Events
- Collect & Weigh study drug

- Assessments
  - *BSA (Affected Body Surface Area)*
  - *PGA*
  - *PASI*

Week 4

- Urine Pregnancy Test *(if applicable)*
- Vital signs with weight
- Concomitant Medication/Treatment
- Physical Exam
- Patient satisfaction survey
- Subject assessment of pruritus VAS
- DLQI
- Drug dispensation / collection
- Adverse Events
- Collect & Weigh study drug
- Assessments
  - *BSA (Affected Body Surface Area)*
  - *PGA*
  - *PASI*

Week 12

- Urine Pregnancy Test *(if applicable)*
- Vital signs with weight
- Concomitant Medication/Treatment
- Physical Exam
- Patient satisfaction survey
- Subject assessment of pruritus VAS
- DLQI
- Drug dispensation / collection
- Adverse Events
- Collect & Weigh study drug
- Assessments
  - *BSA (Affected Body Surface Area)*
  - *PGA*
  - *PASI*

Week 16

- Urine Pregnancy Test *(if applicable)*
- Vital signs with weight
- Concomitant Medication/Treatment
- Physical Exam
- Patient satisfaction survey
- Subject assessment of pruritus VAS
- DLQI
- Drug collection

- Adverse Events
- Collect & Weigh study drug
- Assessments

4.2 Study Treatment

4.2.1 Details of Study Treatment

Enstilar® Foam is a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white foam after evaporation of the propellants. Each gram of Enstilar® Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone).

Enstilar® Foam contains calcipotriene hydrate and betamethasone dipropionate. It is intended for topical use only. Calcipotriene hydrate is a synthetic vitamin D3 analog. Chemically, calcipotriene hydrate is 9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol,24-cyclo-propyl-,monohydrate, (1α,3ß,5Z,7E,22E,24S) with the empirical formula C27H40O3,H20, a molecular weight of 430.6,Calcipotriene hydrate is a white to almost white, crystalline compound. Betamethasone dipropionate is a synthetic corticosteroid. Betamethasone dipropionate has the chemical name pregna-1,4-diene-3,20-dione-9-fluoro-11-hydroxy-16-methyl-17,21-bis(1 oxypropoxy)-(11β,16β), with the empirical formula C28H37FO7, a molecular weight of 504.6, a: Betamethasone dipropionate is a white to almost white crystalline powder. Enstilar® Foam is a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. The propellants used in Enstilar® Foam are dimethyl ether and butane. At administration the product is a white to off-white foam after evaporation of the propellants. Each gram of Enstilar® Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in a base of white petrolatum, PPG-11 stearyl ether, mineral oil, all-rac-alpha-tocopherol, and butylhydroxytoluene.

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Dispensation and Dosage Schedule

A 4-week supply of study medication will be dispensed at baseline and applied daily from weeks 0 to week 4.nd restarted daily at week 12 to week 16. Subjects will be instructed to apply study medication once per day per supplement II.

4.2.2 Treatment Assignment

All subjects who have signed an ICF will receive a 2-digit subject number, starting at 01. This subject number will be used to identify the subject throughout the study. When subjects qualify fo the study, they will be randomized to study treatment groups utilizing treatment assignment numbers (TANs). Therefore, TANs are not the same as subject numbers. The next eligible subject wil

receive the lowest available TAN. The schedule will be prepared on a balanced 1:1 basis and will be available only to the member(s) of the site staff that is responsible for dispensing study treatment to the subject. Subjects withdrawn from the study will retain their subject number and their TAN, if already allocated. New subjects will be allotted a new subject number and, if applicable, a new TAN.

Blinding

Study treatments will be provided to subjects in an open-label manner (the identity of the study treatment will be known by all parties). Investigator will be blinded.

4.2.4 Supplies and Accountability

The Investigator or pharmacist will inventory and acknowledge receipt of all shipments of study medication. All study medication must be kept in a locked area with access restricted to designated study personnel. The study medication must be stored in accordance with the instructions provided with the shipment. The Investigator or pharmacist will also keep accurate records of the quantities of study medication dispensed and returned by each subject.

4.2.5 Treatment Compliance

Subject compliance to study treatment regimen will be assessed at each visit; Patients will be instructed to bring study medication back at each study visit so that cans can be weighed and documented. Study personnel will ask each subject whether they missed any applications of study medication since the previous visit.

4.3 Concomitant Medication/Treatment

Subjects must comply with the restrictions based on prohibited medications and treatments as detailed in the exclusion criteria. Other necessary therapies that will not interfere with the response to treatment may be provided at the discretion of the Investigator. The use of any concurrent medication, prescription or over-the-counter drug, is to be recorded in the source document along with the reason the medication was taken.

5 ASSESSMENTS OF EFFICACY

5.1 Affected Body Surface Area Assessment (BSA)

The area of body affected by psoriasis will be estimated as a percentage of the subjects total body surface area. As means to standardize measurements, the area of the subject's palm will be considered as 1% of total BSA.

5.2 Physician Global Assessment (PGA) – see attached table
The Investigator will grade the current severity of psoriasis as per PGA

6 ASSESSMENTS OF SAFETY

6.1 Safety Assessments

Throughout the study, subjects will be monitored for signs and symptoms of adverse events. All adverse events and con meds will be recorded throughout study. An *adverse event* is any pathological or unintended change in the structure, function or chemistry of the body that occurs during the study, irrespective of causality, including any illness, injury, toxicity, sensitivity, or sudden death. The condition must either not be present pre-study or must worsen in either intensity or frequency during the study. A *serious adverse event* is any untoward medical occurrence, that, at any dose:

- results in death;
- is life-threatening;
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event.

An *unexpected adverse event* is any treatment-related adverse event, which is not identified in nature, severity, or frequency in current literature on the test product.

6.2 Reporting Requirements

6.2.1 Serious and/or Unexpected Adverse Events

Any serious or treatment-related unexpected adverse event occurring in this study must be reported to the IRB within the timelines stipulated by the IRB. In addition, SAEs will be reported to Leo Pharma within 1 (one) business day.

6.2.2 Adverse Event Reporting

All adverse events must be recorded by the Investigator into the CRF. The Investigator will be required to describe the adverse event, onset and stop date, severity, the course of action taken, if any, as well as any pertinent data necessary to allow a complete evaluation of the adverse event. For serious adverse events (SAE), an additional report (SAE report) must be completed.

6.2.3 Follow-up and Final Reports

Subjects who have had a serious adverse event must be followed clinically until all parameters, including laboratory values (if applicable), have either returned to normal or are otherwise explained. If death was the outcome of the event on the initial SAE Report, a Follow-up/Final Report, including autopsy report, when performed, must be completed.

7 STATISTICS

7.1 Sample Size Justification

This is a descriptive study and a formal justification for the sample size. The sample size was calculated based on estimated effect size (proportion of PASI 75) for the two groups and assuming alpha = 0.05 with 80% power (http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-Equality). For this study, effect size was projected as efficacy at week 4: PASI-75 55% for Apremilast (Otezla) +Enstilar® group and 15% for Apremilast (Otezla) + foam vehicle group. With 0.05 alpha and 80% power, we need 19 patients in each group.

7.2 Analyses

Statistical analyses will be conducted on an intent-to-treat population that includes all subjects who were enrolled and received study medication. Due to small sample size and exploratory nature of the study, descriptive statistics will be performed using SAS. Any additional statistical analyses will be performed as appropriate and detailed in the final report. All statistical tests will be two-sided and interpreted at a 5% significance level. Descriptive statistics (i.e., mean, standard deviation, etc.) will be provided for all continuous variables and frequencies for all categorical variables collected in this study. Summary tables will be used to present patient population characteristics at Baseline; data from the study questionnaires will be included. Analyses of study treatment will be performed using an ANCOVA technique with the Baseline value as the covariate provided the necessary assumptions for parametric tests are satisfied. The Wilcoxon Rank-Sum test will be used if the necessary assumptions for parametric tests are not satisfied. Mean scores will also be analyzed. Safety analyses will be performed in terms of incidence and severity of local tolerance signs and symptoms and adverse and/or unexpected events.

8 RESPONSIBILITIES OF THE INVESTIGATOR

8.1 Good Clinical Practice

Investigators must adhere to the procedures outlined in this Study Protocol. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abides by GCP as described in the ICH Guidelines Topic E6: "Guideline for Good Clinical Practice." Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

8.2 Ethics

The appropriate IRB must review the Study Protocol and Informed Consent Form prior to initiating the study. Any significant modifications to the IRB-approved protocol or informed consent must be made in consultation with the IRB.

8.3 Confidentiality of Subjects

Any information that identifies subjects with respect to this research study will be kept confidential. However, records identifying the subject may be inspected by representatives of the IRB and/or the FDA. Subjects' identity will remain strictly confidential during all record reviews, as well as in any publication that may result from this research. Subjects will be identified by study code only; their names will not be used.

8.4 Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Appropriate discussion of risks and possible benefits of this therapy will be provided to the subjects. Consent forms describing in detail the study interventions/products, study procedures and risks will be given to the subject and written documentation of informed consent is required prior to starting intervention/administration study product.

Consent forms will be IRB approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

8.5 Data Handling and Record Keeping

Investigators must ensure that proper source documentation for all study activities are diligently maintained and securely kept. Investigators will transfer all relevant data from source documents to the Case Report Form as stipulated in this Study Protocol and his/her signature on the Case Report Form guarantees completeness and integrity of these data. Investigators will maintain reliable study device dispensing/dosing records and will store study supplies in a secure, locked location. In addition, Investigators will ensure that all study-related source documentation and Case Report Forms will be maintained for a period of two years after the conclusion of the study.

8.6 Direct Access to Source Data/Documents

Investigators must ensure that the Informed Consent Form clearly permit study-related monitoring, audits, IRB review, and regulatory inspections providing direct access to source data and documents.

Physicians Global AssessmentPsoriasis

___ 0. Clear: no signs of psoriasis (Hyper/hypopigmentation changes alone are acceptable). Plaque elevation = 0. Scaling = 0. Erythema = +/- (hyperpigmentation, pigmented macules, diffuse faint pink or red coloration).

___ 1. Almost Clear: Plaque elevation = +/- (possible but difficult to ascertain whether there is slight elevation above normal skin). Scaling = +/- (surface dryness with some white discoloration). Erythema = up to moderate (up to definite red coloration).

___ 2. Mild: Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped). Scaling = fine (fine scale partially or mostly covering lesions). Erythema = up to moderate (up to definite red coloration).

___ 3. Moderate: Plaque elevation = moderate (moderate elevation with rough or sloped edges). Scaling = coarse (coarse scale covering most or all of the lesions). Erythema = moderate (definite red coloration).

___ 4.Severe: Plaque elevation = marked (marked elevation typically with hard or sharp edges). Scaling = coarse (coarse, nontenacious scale predominates, covering most of all lesions). Erythema = severe (very bright red coloration).

Supplement II

Instruct patients to shake can prior to using Enstilar® Foam and to wash their hands after applying the product. Apply Enstilar® Foam to affected areas once daily for 4 weeks. Rub in Enstilar® Foam gently. Discontinue use when control is achieved. Instruct patients not to use more than 60 g every 4 days. Enstilar® Foam should not be used with occlusive dressings unless directed by a physician. Enstilar® Foam is not for oral, ophthalmic, or intravaginal use. Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site.