Protocol for Phase II^b Clinical Trials of Total Coumarin Cream

A PHASE 2B, MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOTAL COUMARIN CREAM IN TREATING PATIENTS WITH PSORIASIS VULGARIS

Protocol Number: 105883-1

Product Name: Total coumarin cream (蛇床子总香豆素软膏®)

Other name: TC Cream

Phase: phase II^b

Sponsored by: Psoriasis Research Institute of Guangzhou (PRIG), China

Version Number: 00

Original date: Jan. 29th, 2015

STATEMENT OF COMPLIANCE

This research will be carried out in accordance with Good Clinical Practice (GCP) as set out by the International Conference on Harmonization (ICH), the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312), and the principles enunciated in the World Medical Association Declaration of Helsinki (Edinburgh, Scotland, 2000). The Investigational New Drug (IND) for the study has been reviewed by the FDA.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CRF	Case Report Form
CRO	Contract Research Organization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
NDA	New Drug Application
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
WHO	World Health Organization

PROTOCOL SYNOPSIS

<table>
<tr><td>Full Title</td><td>A Double-Blind, Randomized, Placebo-Controlled, Multi-Center Phase II^b Clinical Trial to Evaluate the Efficacy and Safety of TC Cream in Treating Patients with Psoriasis Vulgaris</td></tr>
<tr><td>Short Title</td><td>Phase II^b Efficacy and Safety Evaluation of TC Cream in Treating Patients with Psoriasis Vulgaris.</td></tr>
<tr><td>Protocol Number</td><td>105883-1</td></tr>
<tr><td>Clinical Trial Phase</td><td>Phase II^b</td></tr>
<tr><td>IND Sponsor</td><td>Psoriasis Research Institute of Guangzhou, Guangdong, China</td></tr>
<tr><td>Study Centers</td><td>Multi-centers: (1) (2)</td></tr>
<tr><td>Primary Objective</td><td>To observe the efficacy and safety of TC Cream twice daily compared to placebo over 8 weeks in subjects of US population with stable psoriasis.</td></tr>
<tr><td>Secondary Objectives</td><td>To evaluate the effects and improvements of TC Cream on the quality of life in subjects with psoriasis vulgaris (stable stage) based on Psoriasis Disability Index (PDI) and Dermatology Life Quality Index (DLQI); and to determine whether there is further improvement or recurrence of psoriasis after the cessation of TC Cream after 8 weeks treatment of psoriasis vulgaris of stable stage.</td></tr>
<tr><td>Exploratory Objectives</td><td>To investigate and summarize the curative effects and recurrence rate of TC Cream on treated psoriasis patients of US population</td></tr>
<tr><td>Sample Size</td><td>Total: 88 Subjects (44 for the treatment group and 44 for the control group)
<table>
<tr><td rowspan="2">Clinical centers</td><td colspan="2">Stable Stage</td><td rowspan="2">Total</td></tr>
<tr><td>Arm 1
TC</td><td>Arm 2
Vehicle</td></tr>
<tr><td>Center 1</td><td></td><td></td><td></td></tr>
<tr><td>Center 2</td><td></td><td></td><td></td></tr>
<tr><td>Total</td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Study Population</td><td>Male or female patients of 18-70 years old of any race with psoriasis vulgaris of stable stage</td></tr>
<tr><td>Duration of Administration</td><td>8 weeks</td></tr>
<tr><td>Washout</td><td>4 weeks for any topical or systemic corticosteroids, anti-inflammatories, antibiotics, 3-months for any systemic retinoids or biologics, or any investigational treatment</td></tr>
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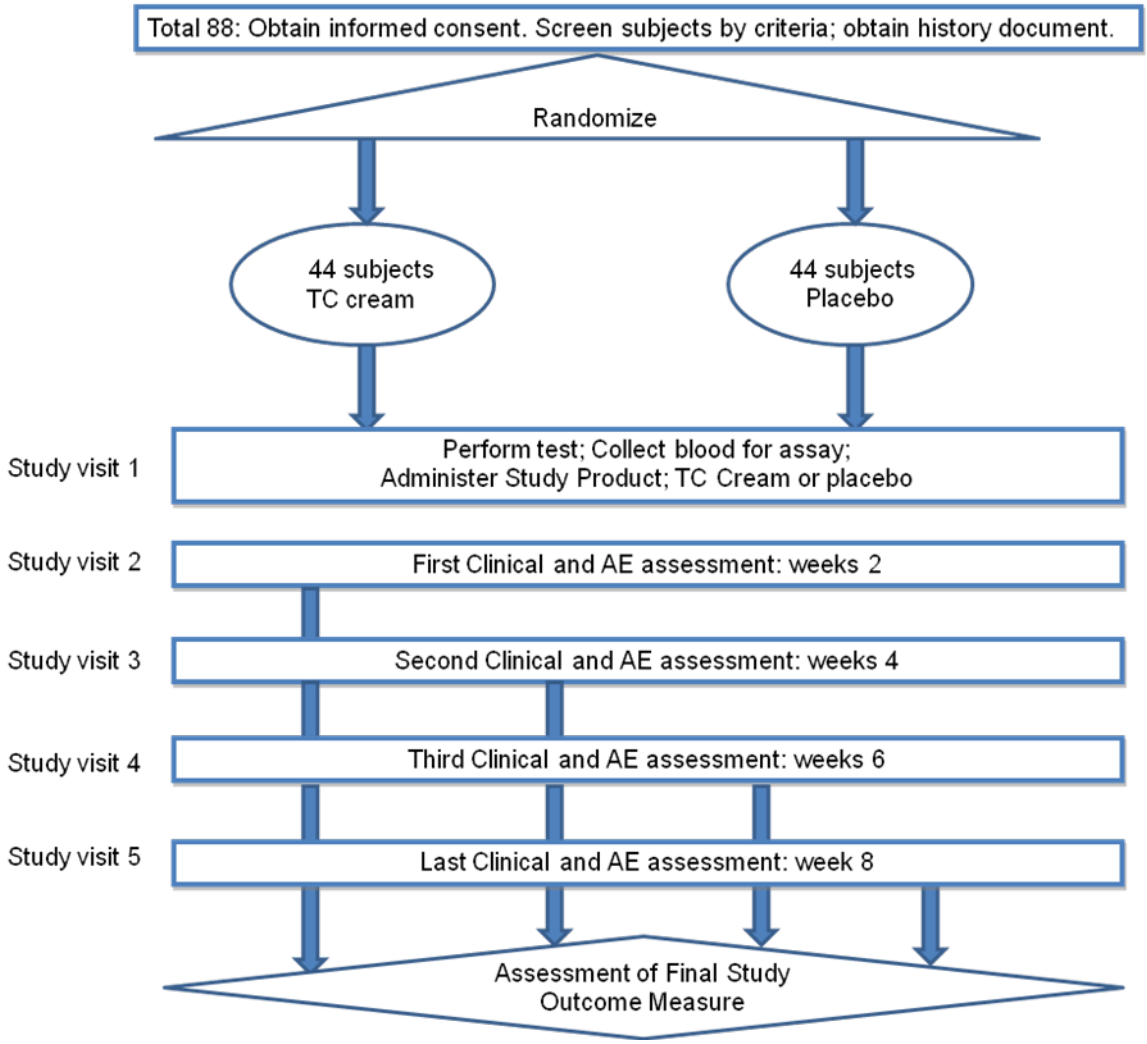
period	
Duration of Study	6 months
Study Design	Multi-center, randomized, double blind (Subject, Investigator), placebo controlled, parallel assignment
Study Agent /Intervention Description	**Treatment group:** TC Cream: 0.3g/cm^2, applied to afflicted area after cleaning the skin with warm water; twice daily (morning and evening); dosage should not exceed 25g/day **Control group (placebo):** Vehicle of TC Cream: 0.3g/cm^2, applied to afflicted area after cleaning the skin with warm water; twice daily (morning and evening); dosage should not exceed 25g/day
Concomitant Medications/ Therapies	None
Safety Considerations and Monitoring of adverse events	Do not expect any side effect other than mild red pigmentation which will disappear after the drug withdrawal.
Diagnosis and Main Inclusion Criteria	✓ Male or female of 18-70 years old ✓ Women of childbearing age must be using birth control strategies defined by one of the following: 1) a barrier method (condom) and 2) oral contraceptives, during the 8-weeks study period. ✓ Consistent with diagnostic criteria of psoriasis vulgaris ✓ ISGA score ≥ 2 (at least mild severity) ✓ BSA (stable stage group): 1% ≤ to ≤20% Note: Randomized, male-female ratio should be properly taken into consideration.
Main Exclusion Criteria	✓ Subjects in pregnancy, preparing for pregnancy or breast feeding ✓ History of hyperergic or photosensitivity ✓ History of complicated cardiovascular disease, cerebrovascular disease, severe primary diseases in hepatic, kidney and hematopoietic system, or patients who are diagnosed with psychotic disorders ✓ Within 2/4 weeks prior to randomization the patients have taken treatment with following approved or investigational psoriasis therapy of the target lesions: o Topical treatments o PUVA, UVB or Grenz ray therapy o Any systemic treatments other than biologicals with a possible effect on psoriasis (e.g., corticosteroids, vitamin D analogues, retinoids, hydroxycarbamide, azathioprine, methotrexate, cyclosporine, other immunosuppressants).

	○ Any types of investigational therapy for psoriasis within the last 30 days ✓ Within 3 months prior to randomization the patients have taken systemic treatment with retinoids or biological therapies (marketed or others) with a possible effect on psoriasis (e.g., alefacept, efalizumab, etanercept, infliximab). ✓ Planned initiation of, or changes to, concomitant medication that could affect psoriasis (e.g., beta blockers, anti-malaria drugs, lithium) during the double-blind phase of the study.
Endpoints	**Observation of Curative Effects:** (1) Severity of local signs - Phenotypes a. Induration (average over all lesions) b. Erythema (average over all lesions) c. Scaling (average over all lesions) （2）Extent - Body Surface Area (BSA) affected （3）Symptoms - Pruritus/itching (average over 24 hours) （4）Visual assessment: Digital photographs on the target skin lesion Note: (1) All patients will be examined and photographed before (first visit) and after (end of the curative treatment) treatment with TC Cream or placebo. (2) The investigator(s) can, not must, consider enrolling the patients may have a lesion on elbow and/or knee. However, the patients who have no lesion on elbow or knee or only have a lesion on one of parts can be enrolled into this research. **Outcome Measures:** • Primary Endpoint: (1) Investigator's Static Global Assessment (ISGA) (2) Assessment of Targeted Lesions • Secondary Endpoint: (1) PASI ≥ 75% improvement • Tertiary Endpoint: (1) Psoriasis Disability Index (PDI) (2) Dermatology Life Quality Index (DLQI) **Statistical Analysis:** Comparison between two groups will be made using the t-test with two-sided 95% confidence interval (CI) for the difference in response rates between the two treatment groups (ITT, TC vs. Vehicle). A P-value< 0.05 is considered to be statistically significant. **Frequency of Evaluation:** – 0 (before treatments), 2, 4, 6 and 8 weeks – After the initial 8 weeks of treatment, there will be a follow up period of 4 weeks during which no treatment is used.

Schematic Flow of Study Design



1. INTRODUCTION

1.1 Background

1.1.1 Study Disease: Psoriasis Vulgaris

Psoriasis is a common, genetically determined, inflammatory, and proliferative skin disease. It is a disabling disease and may even be life-threatening on rare occasions. The duration may vary from a few weeks to a whole lifetime. The clinical course is unpredictable, but in most patients, psoriasis is a chronically remitting and relapsing disease. It has significant social, psychological, and economic consequences. The impact of psoriasis on the quality of life is reported to be comparable with that observed in other chronic medical conditions such as diabetes and depression. Epidemiological studies indicate that psoriasis is associated with other serious conditions such as diabetes, heart disease, and obesity. According to the National Institutes of Health, as many as 7.5 million Americans have psoriasis. Chronic psoriasis vulgaris is the most common form of psoriasis and affects about 90% of patients with psoriasis [1].

Although there is currently no cure for psoriasis, there are three categories of treatment options (Topical, Phototherapy, and Systemic) [2] that can clear psoriasis for a period, yet each treatment has advantages and disadvantages. Ultraviolet light treatment is frequently combined with topical (e.g., coal tar, calcipotriol) or systemic (e.g., retinoids) treatment. Long-term toxicities are observed with all currently available systemic treatments[3,4], such as teratogenic effects and the influence on lipid metabolism with retinoids, cumulative liver toxicity and the risk of bone marrow suppression and of malignancies with methotrexate, hypertension, renal dysfunction, and risk of malignancies with cyclosporine A, and increased risk of squamous-cell carcinoma and melanoma with PUVA therapy. A few new biologics have been developed to treat psoriasis; however, not only are the drug prices extremely high, but they are also often associated with severe adverse effects.

Due to the high frequency of adverse reactions to systemic and Phototherapy, topical agents are often used as first-line therapy for plaque psoriasis. These include salicylic acid, steroids, Vitamin D analogues (such as calcipotriol), tazarotene, dithranol, coal tar extracts, and a combination of any of these agents. Retinoid drugs cause a high rate of irritant reactions on the skin, and as a result, they can only be used in the stable stage of psoriasis; while hormone and immunosuppressive treatments have evident side effects, their short-term efficacy is reasonably good. Recurrence is common after withdrawal of these treatments, and the disease tends to turn into chronic, stubborn, and become more challenging to treat.

1.1.2 Study Agent: TC Cream

TC Cream is a botanical drug developed for the topical treatment of psoriasis vulgaris. It has been proven through phase II and phase III clinical trials conducted in China to have remarkable efficacy and minimal side effects, not only for patients with stable disease but also during flare. It is especially effective for first-time psoriasis patients who have never used any other treatment in the past.

The TC Cream drug product contains a well-characterized plant extract, TC, from a Chinese traditional herb, and a partially purified crystalline powder. It can be used for various skin illnesses. The activity is considered to arise from the whole mixture of the extract, not from an individual component. Drug substance and drug product specifications have two ID tests, including an HPLC method, to achieve effective treatments. So far, the three-month accelerated stability data and long-term (36 months for the drug substance and 45 months for the TC Cream) storage at room temperature have not shown any negative trends. Robust manufacturing of the drug substance and the drug product has been established with tight specifications to assure consistent quality control of the drug product.

1.2 Rationale

TC Cream has been shown to accelerate cutin reduction, reduce inflammation, prevent anaphylaxis and allergy, and exhibit notable antibacterial and anti-pruritic effects through pre-clinical studies and Phase III and Phase II safety and efficacy clinical studies in China. In addition, it can improve the pathological changes of over-proliferation and parakeratosis of epidermal cells in psoriasis.

1.3 Control Agent: Placebo

Vehicle of TC Cream with the same manufacturing formulation and process, without the drug substance added.

1.4 Route of Administration

The study agents are for external/topical use only. Apply a thin layer ($0.3g/cm^2$) of TC Cream to the affected area(s) twice daily. Daily doses exceeding 50g have not been systematically studied.

1.5 Summary of Previous Pre-clinical Studies

1.5.1 Pharmacology

Pharmacological experiments show that TC Cream can inhibit mitosis in the vaginal epithelial cells of mice; it can increase the thickness of the granular layer in the skin scales of rat tails; it has a markedly strong inhibition of passive cutaneous anaphylaxis in

rats. In addition, it significantly inhibits croton oil-induced mouse ear swelling and albumin-induced rat paw edema and evidently raises the itch threshold to histamine phosphate in guinea pigs. Research shows that TC Cream promotes cutin reduction, anti-inflammation, anti-anaphylaxis, and anti-allergy effects, as well as notable antibacterial and antipruritic effects. Besides, it can improve the pathological changes of over-proliferation and parakeratosis of epidermal cells in psoriasis. It is an effective psoriasis treatment.

1.5.2 Toxicology

2. OBJECTIVES

- To observe the efficacy and safety of TC Cream twice daily compared to placebo over 8 weeks in subjects of the US population of patients with psoriasis vulgaris (stable stage) based on Investigator's Static Global Assessment (ISGA), Target Lesion, Psoriasis Area and Severity Index (PASI).
- To evaluate the effects and improvements of TC Cream on the quality of life in subjects with psoriasis vulgaris based on Psoriasis Disability Index (PDI) and Dermatology Life Quality Index (DLQI), and to determine whether there is further improvement or recurrence of psoriasis after the cessation of TC Cream after 8 weeks of treatment for psoriasis.
- To investigate and summarize the curative effect and recurrence rate of TC Cream on treated psoriasis patients of the US population.

3. STUDY DESIGNS

This is a double-blind, randomized, placebo-controlled, parallel-controlled, multi-center, phase II^b clinical trial.

This phase II^b clinical trial includes two study groups: a treatment group and a placebo

group, and it will be conducted at multiple centers. The total number of sample cases needed for this trial is 88 patients enrolled. The subjects are both inpatients and outpatients with BSA ≥1% to ≤20%. Approximate time to complete study enrollment is 1～2 days. The expected duration of subject participation is 8 weeks. After the initial 8 weeks of treatment, there will be a 4-week follow-up period during which no treatment is used.

3.1 Randomization

Subjects will be randomly assigned to a treatment agent according to a predetermined computer-generated randomization scheme.

Subjects will be assigned consecutive subject numbers in ascending order. This number will identify the subject and determine the treatment of drug product administration according to the randomization scheme.

3.2 Blinding

Double blinding: the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) will be blinded from the treatment agents throughout the study.

3.3 Patient Selection

3.3.1 Study Population

The study will include psoriasis patients in the US population.

3.3.2 Sample Size

A total of 88 subjects in the study centers will be included.

3.3.3 Screening Procedures

Screening procedures will include the following:

- medical history
- vital signs (blood pressure, pulse rate, respiration, and temperature)
- demographic data collection and measurements of height and weight
- photocopies of the affected skin
- physical examination.

3.3.4 Inclusion Criteria

- Age of 18-70 years old. Both men and women, and members of all races and ethnic groups, will be included
- Consistent with the diagnostic criteria of stable-stage psoriasis vulgaris, and have at least two target lesions suitable for evaluation

- Women of childbearing age must be using birth control strategies defined by one of the following: 1) a barrier method (condom) and 2) oral contraceptives, during the 8-week study period.
- ISGA score ≥ 2 (at least mild severity)
- BSA (stable stage group): 1%≤ to ≤20%
- Signed a written informed consent document
- No additional exposure to the sun

Note: Randomized, male-female ratio should be adequately taken into consideration.

3.3.5 Exclusion Criteria

- Subjects in pregnancy, preparing for pregnancy, or breastfeeding
- History of hyperergic or photosensitivity
- History of complicated cardiovascular disease, cerebrovascular disease, severe primary diseases of hepatic, renal, and hematopoietic systems, or patients who are diagnosed with psychotic disorders
- History of photosensitive diseases such as porphyria, chronic actinic dermatitis, Xeroderma
- Within 2/4 weeks before randomization, the patients have taken treatments with the following approved or investigational psoriasis therapy of the target lesions:
    - Topical treatments
    - PUVA, UVB, or Grenz ray therapy.
    - Any systemic treatments other than biologicals with a possible effect on psoriasis (e.g., corticosteroids, vitamin D analogues, retinoids, hydroxycarbamide, azathioprine, methotrexate, cyclosporine, other immunosuppressants).
    - Any other type of investigational therapy for psoriasis
- Within 3 months before randomization, patients have received systemic retinoid or biological therapy (marketed or otherwise) that may affect psoriasis (e.g., alefacept, efalizumab, etanercept, infliximab).
- Planned initiation of, or changes to, concomitant medication that could affect psoriasis (e.g., beta blockers, anti-malaria drugs, lithium) during the double-blind phase of the study.
- The history of allergic reactions attributed to similar dermatological drugs are excluded according to specific cases decided by investigators

3.3.6 Washout Period

- 4-weeks for any topical or systemic corticosteroids, anti-inflammatories, antibiotics,
- 3-months for any systemic retinoids or biologics, or any investigational treatment
- Only specific procedures are performed as indicated in the table of Schedules of

Events, if subjects need washout periods

3.4 Treatment Plan

3.4.1 Administration

3.4.1.1 Treatment group:
TC Cream: 0.3g/cm^2, applied to the afflicted area after cleaning the skin with warm water; twice daily (morning and evening); dosage should not exceed 25g/day.

3.4.1.2 Control group (placebo):
Vehicle of TC Cream: 0.3g/cm^2, applied to the afflicted area after cleaning the skin with warm water; twice daily (morning and evening); dosage should not exceed 25g/day.

3.4.2 Duration of Therapy

Subjects should continuously apply the study agent twice daily (morning and evening) for 8 weeks. 4 weeks after treatment is completed, patients are required to return for study follow-up.

3.4.3 Treatment Compliance

The participants will be instructed to return all unused or part-used medication and packaging from used medication at each visit. The Investigator may withdraw participants if they consider compliance unsatisfactory.

3.4.4 Concomitant Drug Treatment

The subjects can use emollients (non-medicated moisturizers) during the study, but not on the day of the visit.

Subjects enrolled in this study will not be taking concomitant medications for other diseases.

If drug therapy for other diseases is required during the study, the investigator/study director will decide whether to continue or discontinue the subject's participation, and any corresponding medications should be recorded.

3.4.5 Early Withdrawal of Subjects

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Voluntary patient withdrawal
- The investigator's decision that it is in the patient's best interest to withdraw
- If the patient becomes pregnant

- Noncompliance
- Significant protocol violation
- Safety reasons if any of the following occur:
  - Disease progression
  - Intercurrent illness that prevents further administration of treatment
  - Unacceptable adverse events(s)
  - Patient decides to withdraw from the study, or
  - General or specific changes in the patient's condition render the patient unacceptable for further treatment in the investigator's judgment.
- For any reason, at the Sponsor's or Investigators' discretion

3.5 Agent Formulation and Procurement

3.5.1 Agents Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent.

At the completion of the study, all unused study drug(s) will be returned to the sponsor unless authorized by the sponsor for appropriate disposal.

3.5.2 Study Agents Supply

The sponsor (PRIG) will supply sufficient quantities of the study drugs to allow completion of this study. Study agents (test and control) are supplied in identical 25g collapsible tubes.

Designated clinical staff will be responsible for monitoring the receipt, storage, dispensing, and accounting for all study medications in accordance with Good Clinical Practice (GCP) and FDA regulations.

The appearance and packaging of the placebo will be consistent with those of the investigational product. The subjects and the investigators couldn't distinguish them. The product name, strength, the manufacturer's name, and lot/batch number will be identified on each container. The control agent will also include an expiry date. The study drugs will be placed under appropriate storage conditions in an area with controlled access.

Every subject will receive a packaging kit; exterior and interior packages should be kept with their respective labels.

3.5.3 Storage Conditions

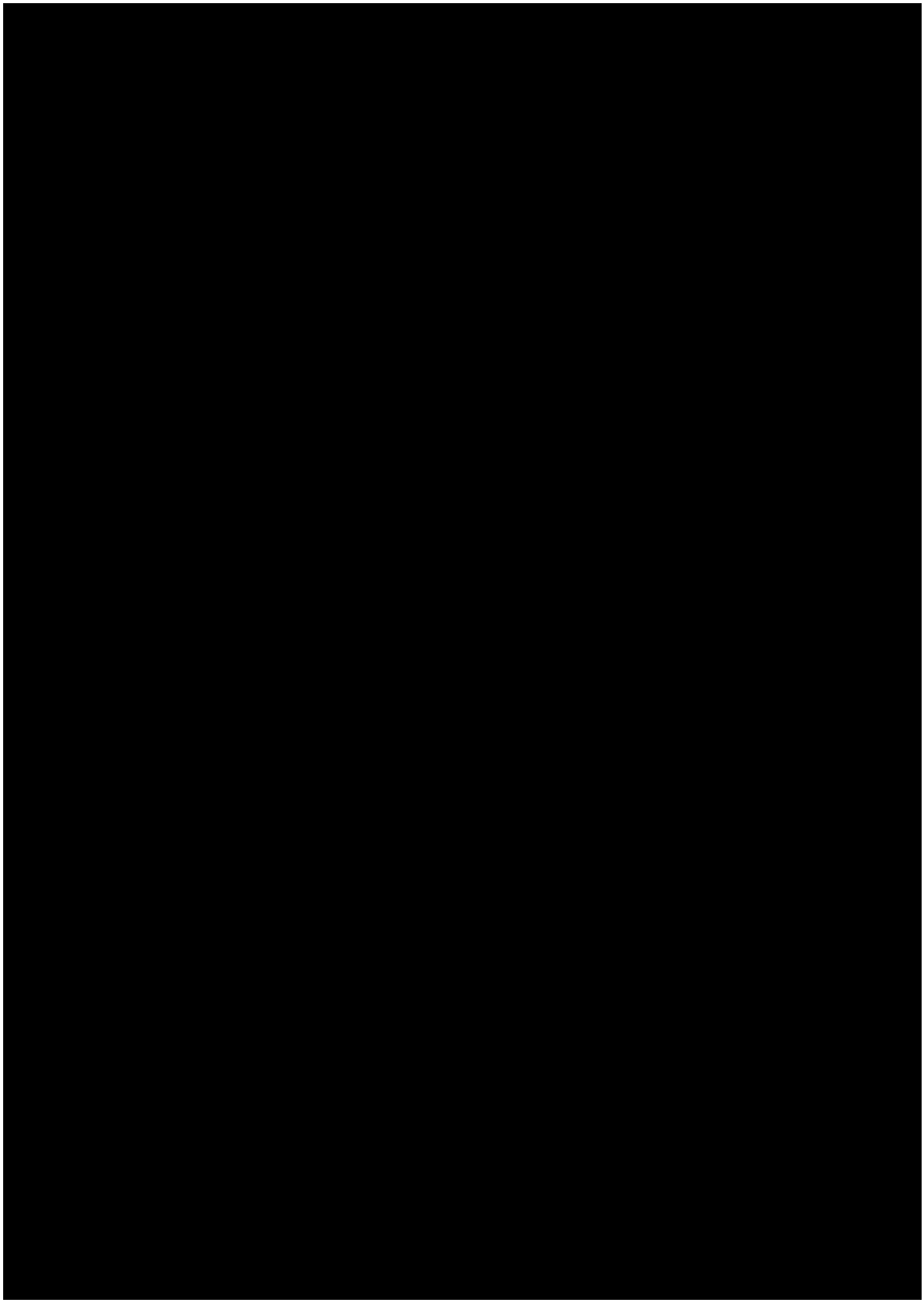
Store at room temperature 15º C - 25º C (59º F - 77º F). Do not freeze. Keep tightly closed and away from light. Keep out of reach of children.

3.5.4 Stability

The study agent (both drug substance and finished product) is stable for at least 36 months at room temperature in shaded places

4. STUDY PROCEDURES AND SCHEDULE OF EVENTS

4.1 Schedule of Events



[redacted]

4.2 Observations of Curative Effects

The following symptoms should be observed and documented for evaluation:

[redacted]

4.3 Scoring of Clinical Symptoms

4.3.1 Severity of local signs - Phenotypes

a) Induration (elevation)

The NPF induration card is to be used to assist the induration assessments.

Table 1 Induration (average over all lesions)

[redacted]

b) Erythema (Redness)

Table 2 Erythema (average over all lesions)

[redacted]

3	Moderate	reddish patchy coloration
4	Severe	bright red coloration
5	Very severe	dusky to deep red coloration

c) Scaling

Table 3 Scaling (average over all lesions)

[redacted]

4.3.2 Extent - Body Surface Area (BSA) Affected

[redacted]

Figure 1 Square Ruler of 9cm x 9cm

4.3.3 Symptoms - Pruritus (Itching)

Table 5 Patient Assessment of Itching/Pruritis

5. MEASUREMENT OF EFFECT

5.1 Clinical End Points

Clinical outcomes will be evaluated by following the criteria:

1. Primary Endpoint:
    (1) Investigator's Static Global Assessment (ISGA)
    (2) Assessment of Target Lesions
2. Secondary Endpoint:
    (1) PASI≥ 75% improvement
3. Tertiary Endpoint:
    (1) Psoriasis Disability Index (PDI)
    (2) Dermatology Life Quality Index (DLQI).

For the purposes of this study, patients should be evaluated at baseline (0) and reevaluated for response at 2, 4, 6, and 8 weeks. In addition, a rebound evaluation should also be obtained 4 weeks after the final evaluation of week 8.

The efficacy evaluation of all outcomes will be static ordinal, integer-valued, and scaled (e.g., success or failure), where 'success' involves a score of Clear/Almost Clear and a 2-grade improvement.

5.1.1 Investigator's Static Global Assessment（ISGA）Scale Definition

Table 6 Investigator's Static Global Assessment (ISGA) Scale Definition

Score	Grade	Definition
0	None	No plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale; no itching. Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale) Erythema = ± (hyperpigmentation, pigmented macules, diffuse faint pink or red coloration)
1	Minimal	Essentially flat with possible trace elevation; faint erythema; no psoriatic scale Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = ± (surface dryness with some white coloration) Erythema = up to moderate (up to definite red coloration) Majority of lesions have individual scores for induration, erythema, scaling, BSA and Pruritus (as described above) that average 1.
2	Mild	Slight plaque elevation, scaling, and/or erythema. 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) Majority of lesions have individual scores for induration, erythema, scaling,

		BSA and Pruritus (as described above) that average 2.
3	Moderate	Moderate plaque elevation, scaling, and/or erythema. Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (coarse scale covering most of all of the lesions) Erythema = moderate (definite red coloration) Majority of lesions have individual scores for induration, erythema, scaling, BSA and Pruritus (as described above) that average 3.
4	Severe	Marked plaque elevation, scaling, and/or erythema. Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (coarse, non-tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration) Majority of lesions have individual scores for induration, erythema, scaling, BSA and Pruritus (as described above) that average 4.
5	Very Severe	Very marked plaque elevation, scaling, and/or erythema. Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration) Majority of lesions have individual scores for induration, erythema, scaling, BSA and Pruritus (as described above) that average 5.

Efficacy Evaluation:

Success = [Baseline (ISGA ≥2) – follow-up ISGA score] ≥ 2, meaning:

- Patients with “mild” psoriasis become “clear”.
- Patients with “moderate” psoriasis become “clear” or “almost clear”.
- Patients with “severe” psoriasis become at least “mild”, if not “clear” or “almost clear”.
- Patients with “very severe” psoriasis become at least “moderate” if not mild to clear.

5.1.2 Target Lesion

Pre-select two target lesions representative of the disease (for example: one from a refractory area, elbow or knee, while the other from the trunk) for separate variables, including induration, erythema, scaling, and BSA on a 6-point score.
Take photographs and measure the severity and extent before the clinical intervention and at every visit.

Effective (average of 2 Target Lesions) = [Baseline (Target Lesions≥2) - Target Lesions

score at end of treatment] ≥2.

The response to TC Cream will be assessed relative to the placebo group (ratio of patients who achieved the efficacy goal).

Table 7. Severity of Psoriasis Area Severity Index (PASI) at the Target Lesion Site

Score	Grade	Erythema	Scaling	Plaque Elevation
0	Clear	No evidence of erythema	No evidence of scaling	No evidence of plaques above normal skin level
1	Almost Clear	Pink discoloration, minimal erythema	Occasional fine scales hardly noticeable	Slight, just discernable elevation above normal skin level
2	Mild	Light red coloration	Slight but definite roughness, fine scale present, no cracking	Discernable elevation above normal skin level upon examination, but not pronounced
3	Moderate	Moderate redness, but not dark	Moderate roughness, somewhat coarse scaling	Definite plaque formation with rounded/sloped edges to plaque
4	Severe	Dark red coloration	Marked roughness, coarse/thick scaling, cracking may be evident	Marked elevation with hard, distinct edges to plaque
5	Very Severe	Very dark red coloration with induration present	Very thick scales covering extensive area severe cracking/fissures may be evident	Very marked elevation, very hard and sharp edges to plaque

Note: Body Surface Area (BSA) percentage is no longer requested as an individual component sign in the PASI scale, but the BSA percentage and distribution should be recorded at baseline.

5.1.3 Psoriasis Area and Severity Index (PASI)

PASI is a physician-performed assessment of both the extent of psoriasis on the four body areas (head, trunk, upper limbs, and lower limbs) and the degree of plaque erythema, scaling, and thickness. The PASI score accounts for both the extent of BSA affected by erythema, scaling, and thickness, and the severity of erythema, ranging from 0 (no disease) to 72 (maximal disease).

The proportion of subjects achieving PASI 75, defined as ≥ 75% improvement in PASI score from baseline at the end of 8 weeks of treatment, is the secondary efficacy endpoint

in this study.
(See attached PASI scoring template)

5.1.4 Psoriasis Disability Index（PDI）

The Psoriasis Disability Index questionnaire was developed by Cardiff University's Dermatology Department in Wales, UK, to assess quality of life in patients with Psoriasis. It is self-explanatory and can be handed to the patient to fill in, without the need for a detailed explanation. It is usually completed in three or four minutes

Scoring (Visual Analogue Scale)

The scoring of each question is answered on a graded scale from 0 to 6. If a question is left unanswered, the score taken is 0. The PDI is calculated by summing the scores of the fifteen questions, resulting in a maximum of 90 and a minimum of 0. The higher the score, the greater the impairment of quality of life. The PDI can also be expressed as a percentage of the maximum possible score of 90.

Scoring (Tick-box method)

The scoring of each question is answered on a series of 4 answers: not at all (scores 0), a little (scores 1), a lot (scores 2), very much (scores 3). If a question is left unanswered, the score taken is 0. The PDI is calculated by summing the scores of the 15 questions, resulting in a maximum of 45 and a minimum of 0. The higher the score, the greater the impairment of quality of life. The PDI can also be expressed as a percentage of the maximum possible score of 45.

The PDI can be analyzed under five headings as follows

		VAS	**Tick-Box**
Daily Activities	Questions 1，2，3，4，5	Score max：30	15
Work or School or alternative questions	Questions6，7，8	Score max：18	9
Personal relationships	Questions 9，10	Score max：12	6
Leisure	Questions 11，12，13，14	Score max：24	12
Treatment	Questions 15	Score max：6	3

See attached PDI questionnaire.

5.1.5 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is the most widely used measure for assessing quality of life related to skin disease in psoriasis trials. This tool consists of 10 questions covering six domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and trouble with psoriasis treatment). The response options range numerically from 0 to 3 points, with 0 indicating not affected at all and 3 indicating very much affected. This yields an overall score of 0–30 points, with lower scores indicating better quality of life. (See attached QLDI questionnaire.)

Table 8. Dermatology Life Quality Index (DLQI) Scale Definition

Score	Definition
0 to 1	No impact
2 to 5	Mild impact
6 to 10	Moderate impact
11 to 20	Very large Impact
21 to 30	Extremely large impact

5.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using the supplied 9x9 square ruler and camera. All baseline evaluations should be performed as close to the beginning of treatment as possible, and no more than 1 week before the beginning of treatment.

The same assessment method and technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

6. SAFETY

6.1 Expected Adverse Events

In the multiple controlled randomized clinical trials conducted in China, the most frequent adverse experiences reported with TC Cream were mild skin pigmentation (mild color pigmentation, erythema); very few patients had mild chromatosis or photosensitivity. The symptoms will usually disappear with drug withdrawal. No severe adverse reactions were reported in the completed clinical studies.

6.2 Adverse Event Definition and Classification

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether related to the medicinal (investigational) product.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cTC.htm.

6.3 Serious Adverse Event

A serious adverse event (SAE) is defined as any adverse experience that results in any of the following outcomes:

- Fatal
- Life-threatening
- Requires or prolongs hospitalization
- Results in persistent or significant disability or incapacity；
- A congenital anomaly or birth defect
- An important medical event requires medical intervention to prevent one of the above outcomes.

Important medical events are those that may not be immediately life-threatening but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization. These adverse events will generally be considered serious by this criterion.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of the AE, or that they occurred because of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened, or to diagnostic procedures.

6.4 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

The clinical investigator will review any abnormal laboratory changes and, if any additional action is taken (e.g., reducing the dose or stopping the drug), report the laboratory abnormality as an adverse event on an Adverse Event case report form.

6.5 Pregnancy

Any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded and followed up for congenital abnormalities or birth defects. Pregnancy tests will be performed three times using test strips at pre-study -1 (or week 0), 4, and 8. Birth control strategies should be used for age-bearing female patients.

6.6 Severity of Adverse Events

Adverse events will be classified according to the following severity scale:

- Grade 1(Mild) - The adverse event is easily tolerated and does not interfere with daily activity.
- Grade 2 (Moderate) - The adverse event interferes with daily activity, but the subject

is still able to function.

- Grade 3 (Severe) - The adverse event is incapacitating and requires medical intervention.

6.7 Relationship to Study Drug

Adverse events will be assessed for the relationship to the study drug (causality) according to the following scale:

Unrelated - The event is independent of the study drug.

Unlikely - The event may or may not follow a reasonable temporal sequence from drug administration and can plausibly be explained and/or attributed to something other than the study drug.

Possible - The event follows a reasonable temporal sequence from drug administration, follows a clinically reasonable response on withdrawal, and is unlikely to be attributed to something other than the study drug.

Probable - The event follows a reasonable temporal sequence from drug administration, follows a clinically reasonable response on withdrawal, and cannot be reasonably explained by something other than the study drug.

Definite - There is clear evidence to reveal causality, and other possible existing factors can be excluded. It follows a reasonable temporal sequence from the time of drug administration. It follows a known response pattern to the suspected drug. It disappears on cessation and recurs with reintroduction of the test drug.

6.8 Procedures for Collecting Adverse Event Information

Before subsequent drug administration(s), subjects will be questioned concerning unusual symptoms that may have occurred since the previous administration of the study drug(s).

Any adverse events, whether serious or non-serious, will be monitored throughout the study and followed to resolution, when possible, regardless of whether the subject is still participating in the study. The investigator will remain on-call until the end of the study.

6.9 Procedures for Reporting Adverse Events

Subjects will be instructed to report any adverse events that may arise during the study to clinic personnel.

All symptoms will be recorded and will be reviewed by the investigator before any subsequent drug administration.

When appropriate, medical tests and examinations will be performed to document resolution of the event(s).

Adverse events will be classified according to the MedDRA (Medical Dictionary for

Regulatory Activities) and reported by severity, duration, relationship to the study medication(s), and action taken.

All serious adverse events occurring during the study, whether considered to be related to the study drug, will be reported to Teva within 48 hours. SAE report(s) will be typed in English.
These SAE reports will contain the following information:

A. Study name/number
B. Study Drug
C. Investigator details (name, phone, fax, e-mail)
D. Subject Number
E. Subject Initials
F. Subject Demographics
G. Clinical Event
1) Description
2) Date of onset
3) Treatment (drug, dose, dosage form)
4) Relationship to study drug
5) Action taken regarding the study drug
H. If the AE was Fatal
1) Cause of death (whether the death was related to the study drug)
2) Autopsy findings (if available).

The notification about any serious adverse event will be directed to the Sponsor.

7. DROPOUT, WITHDRAWAL, AND TERMINATION

If a subject's participation is terminated prematurely, the cause for the early termination will be documented.

Subjects will be free to drop out or withdraw at any time, for any reason, or they may be dismissed, if necessary, to protect their health or the integrity of the study.

Subjects who experience worsening of their skin condition will be evaluated for continued participation in the study based on the potential impact of the TC Cream on the integrity of the study results and the current FDA guidelines. The evaluation will take place as soon as possible after the episode(s) occurred.

Subjects who have a medical event equivalent to CTCAE grade 2 or higher infection that is deemed not suitable for continuation of the treatment may be considered to withdraw from the trial (as determined by the investigator).

8. DATA MANAGEMENT

8.1 Fill in CRF

The case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. **DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.**

8.2 Data Entry and Amendment

The data administrator, appointed by the sponsor, is responsible for data entry and management. All study data will be entered on the EpiData 3.1 Software. To vouch for the accuracy of the data, the data should be entered by two data entry staff to create duplicate copies, then the data administrator conducts proofing, scanning, and reporting on two copies of the database.

For existing CRE questions, data management will produce a question-and-answer form and request it from the investigator through the clinical monitor. The investigator should answer the questions and return as quickly as possible. Data management conducts data amending, affirming, and inputting according to the investigator's responses. It could revert to a question-and-answer format if necessary.

8.3 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff to ensure they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site PI or designee.
Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete and accurate documentation.

The Data Coordinating Center will serve as the Statistical and Data Coordinating Center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1 Sample Size Assumptions

The sample size of the investigational product must be up to 44 cases, and the placebo must be 44 cases (total sample size 88 cases). In this way, it can be deduced that the treatment group's efficiency is better than that of the placebo group, assuming a 90% single-sided testing efficiency.

[redacted]

9.2 Data Analysis Considerations

9.2.1 Efficacy Analysis Populations

The populations include all patients who were randomized and received at least one dose of any study drug.

9.2.2 Safety Analysis Populations

The populations include all patients who were randomized and received at least one dose of any study drug.

9.2.3 Analysis Data Sets

A. Intention-to-treat (ITT) Analysis should be defined as all subjects randomized and dispensed medication. Subjects should not be excluded from the ITT population for dropping out or failing to follow the protocol.
B. Safety Analysis Sets are performed for all patients who underwent randomization and received at least 1 dose of study medication. So, with or without a test record, patients who experience adverse events should be included in the statistical analysis if they have received at least one dose of the study medication.

9.2.4 Analysis Plan

The response to treatment with TC Cream will be assessed using an intention-to-treat (ITT) comparison with the placebo group (ratio of efficacy goals achieved).

The statistical analysis will be performed using a two-sided t-test with a 95% confidence interval (CI) for the difference in response rates between the two treatment groups (ITT, TC vs. Vehicle). A P value < 0.05 is considered to be statistically significant.

9.2.4.1 Efficacy Analyses

The data will be summarized with descriptive statistics, including Demographics, baseline, and each efficacy endpoint. The measurement data will be described by its mean, standard deviation, minimum, and maximum, and the 95% confidence interval for the mean will be calculated. The enumeration data will be described by its frequency and percentage, and the 95% confidence interval of the percentage will be calculated.

9.2.4.2 Safety Analyses

The safety data will be summarized with descriptive statistics.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and applicable regulatory requirements. The investigator can delegate tasks to qualified designees.

10.2 Ethical Review

An investigator will not initiate a study without written approval from the Institutional Review Board (IRB). This protocol and the Informed Consent Form (ICF) will be reviewed and approved by the IRB prior to the initiation of the study. Any amendments to the protocol will also be reviewed by the IRB. A copy of the IRB's approval documentation will be included in the final report.

The IRB is constituted and operates in accordance with the principles and requirements described in the U.S. 21 CFR Part 56, and the ICH Harmonized Tripartite Guideline

10.3 Informed Consent

Written informed consent will be obtained from all patients or their legally authorized representative participating in this trial, as stated in the Informed Consent section of the Federal Regulations, Title 21, Part 50. If a patient's signature cannot be obtained, for all patients under the age of 18, the investigator must ensure that the patient's legally authorized representative signs the informed consent. Prior to signing the ICF, subjects will be allowed adequate time to consider the potential risks associated with their participation in the study. A copy of the signed ICF will be provided to the subject. Documentation of the consent process and a copy of the signed consent shall be maintained in the patient's medical record.

10.4 Confidentiality

All documentation collected by the sponsor or by the investigator will be kept confidential and remain the property of the sponsor.

10.5 Amendments and Protocol Revisions

Amendments to the protocol or the ICF will be submitted to the IRB for approval. Any modification to this protocol will be documented as a protocol revision or amendment, signed by the principal investigator and approved by the IRB before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the patient. In such cases, the investigator must notify the IRB in

writing within 10 working days after the implementation. PRIG confirms that any substantive major changes to the protocol will be notified to the FDA.

For amendments to the protocol that alter the study design after the study has been initiated, the investigator and/or the sponsor will decide whether the subjects' consent to continue participation is required. If an alteration is required to the ICF, subjects will be asked to sign the revised ICF at their next visit.

10.6 Study Termination

The sponsor (PRIG) reserves the right to terminate the study at any time.

11. MONITORING OF THE STUDY

11.1 On-Site Audits/Inspections

Representatives of the sponsor will visit the clinical research facility to conduct an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, study medication, and source documents (CRFs) for inspection and comparison. The sponsor will provide sufficient notice to the clinical facility prior to the visit to allow adequate preparation for the audit.

Similar inspection procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a New Drug Application. The clinical facility will immediately notify the sponsor if a regulatory agency contacts it regarding an upcoming inspection.

11.2 Monitoring

The sponsor or representative(s) of the sponsor may visit the study site to monitor the conduct of the study. The staff of the clinical facility will be available to assist the sponsor in answering any inquiries.

During these monitoring visits, the subjects' medical records, CRFs, and other study-related documents, including drug accountability records and study medications, will be made available for review.

12. ARCHIVES/RECORD RETENTION

The clinical facility will archive all study-related documents and retain test and reference products in accordance with applicable regulatory requirements.

If the investigator(s) relocate or, for any reason, withdraw from the study, the study

records must be transferred to an agreed-upon designee, such as another institution, another investigator, or to Psoriasis Research Institute of Guangzhou, Guangdong, China (PRIG). Records must be maintained in accordance with PRIG or FDA requirements.

13. REFERENCES

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