Official Title: An Open-Label, Real World Study Evaluating the Long-Term Quality of Life of Tildrakizumab in Adult Patients With Moderate to Severe Plaque Psoriasis

Document: Clinical Study Protocol

NCT number: NCT03718299

Date: 2 January 2020

CLINICAL STUDY PROTOCOL v1.3

[redacted]

An Open-Label, Real World Study Evaluating the Long-Term Quality of Life of Tildrakizumab in Adult Patients with Moderate to Severe Plaque Psoriasis

Protocol Number:	TIL2018-1
Test Product:	Tildrakizumab
Indication:	Psoriasis
Sponsor:	Sun Pharma Global FZE Office No. 43, Block Y, SAIF Zone, P.O. Box No. 122304, Sharjah United Arab Emirates
Development Phase:	Phase 4
Sponsor Signatory:	[redacted]
Sponsor Medical Monitor:	[redacted]
Sponsor Representatives:	Anna Houlihan Project Manager Sun Pharmaceuticals Industries Inc.
[redacted]	[redacted]
[redacted]	[redacted]
Date of Current Protocol:	2 January 2020

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Pharmaceuticals Industries, Inc except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

[redacted]

[redacted]

PROTOCOL SYNOPSIS

Title	An Open-Label, Real World Study Evaluating the Long-Term Quality of Life of Tildrakizumab in Adult Patients with Moderate to Severe Plaque Psoriasis
Protocol Number	TIL2018-1
Development Phase	4
Investigational Product	Tildrakizumab; supplied as a pre-filled syringe (PFS) and administered [redacted] Each PFS contains 100 mg of tildrakizumab [redacted].
Study Objectives	The primary objective is to demonstrate improvement in subject quality of life (QOL) during and after treatment with tildrakizumab under real world conditions as measured by Psychological General Well-Being scale (PGWB). Secondary objectives include assessment of patient quality of life as measured by Dermatology Life Quality Index (DLQI), psoriasis symptom control, patient satisfaction, long-term efficacy and safety.
Study Design	Uncontrolled open-label, single arm, multicenter study design
Treatment Groups	All subjects will receive tildrakizumab 100 mg [redacted] at Week 0, Week 4, Week 16, Week 28, Week 40 and Week 52.
Duration of Treatment	Injections of tildrakizumab will be given at Week 0, Week 4, Week 16, Week 28, Week 40 and Week 52
Estimated Duration of the Study	Each subject's participation: Approximately 64 weeks Total study duration: dependent upon rate of recruitment.
[redacted]	[redacted]
Total Number of Subjects	Approximately 60 subjects will be enrolled
Number of Sites	Approximately 2
Inclusion Criteria	1. Subjects are non-immunocompromised males or females 18 years of age or older. 2. Subjects have ≥3% total body surface area plaque psoriasis. 3. Subjects are candidates for phototherapy or systemic therapy. 4. Subject must be diagnosed at least 6 months prior to entering the study. 5. Females must be surgically steriliz[redacted], postmenopausal for >5 years, or using a highly effective form of birth control (<1% failure rate) [2,3], for at least 30 days

[redacted]

	prior to test article exposure, with a negative serum pregnancy test at Screening . [redacted]

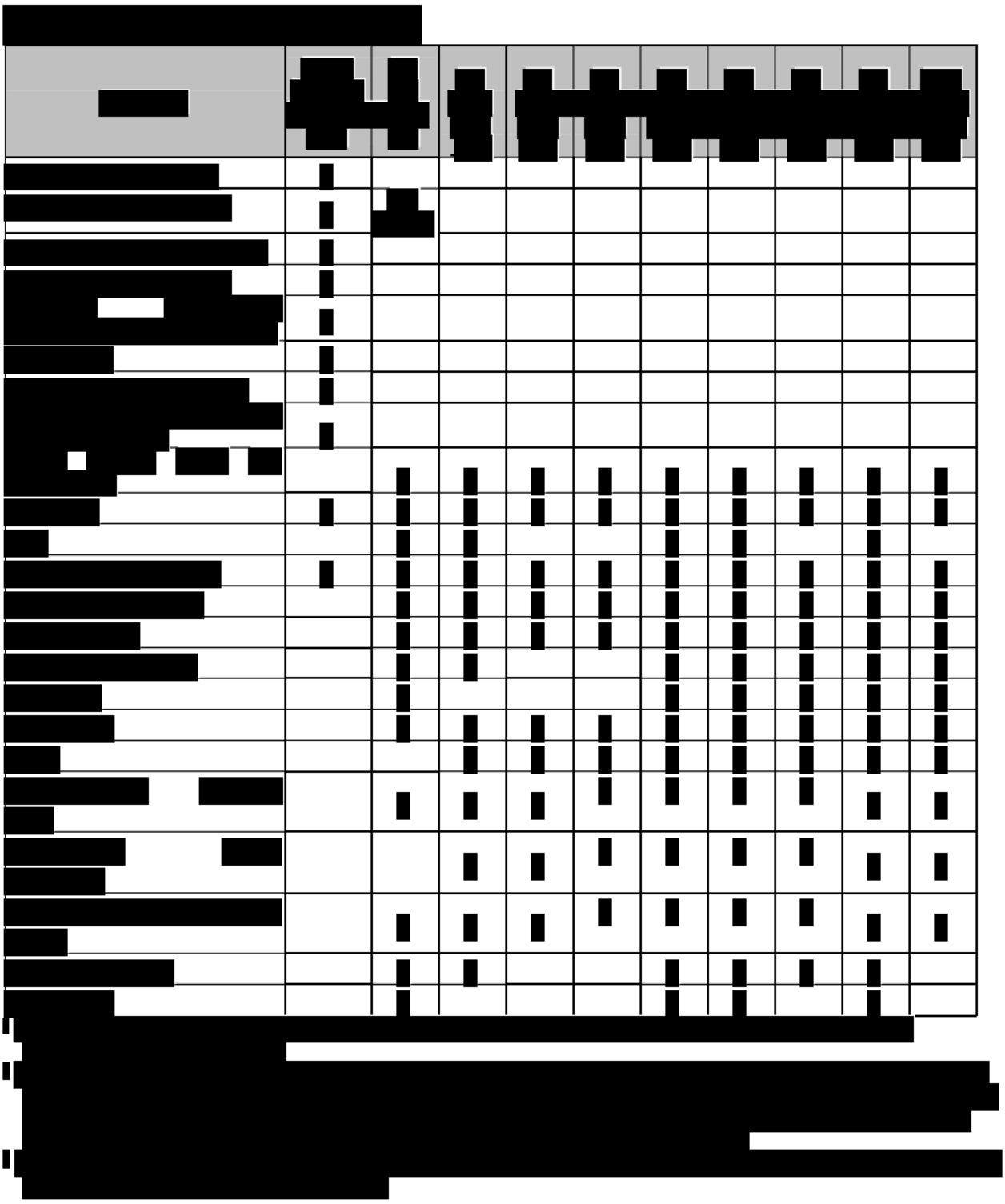
Exclusion Criteria	1. Subject is pregnant, lactating, or is planning to become pregnant during the study. 2. Subject is younger than 18 years of age. [redacted] 7. Subjects with uncontrolled mental illness or active suicidal ideations based on mental health questionnaire of choice. [redacted] Subject is known, or suspected of being unable to comply with the study protocol, in the opinion of the investigator. Subject is currently enrolled in an investigational drug or device study. [redacted]

	[redacted]
Study Procedures	The following procedures will take place according to the visit schedule. [redacted] Study procedures will be explained by the study coordinator and the subject will provide signed, written informed consent. Consent must be signed prior to the initiation of any study-related procedures. Subjects will be asked whether they are willing to be contacted by a representative of the Sponsor to share their experience. Inclusion/Exclusion (I/E) criteria will be reviewed to determine subject eligibility. Demographic information, medical history including review of concomitant medications and psoriasis treatment history, full physical exam including psoriasis assessments, clinical laboratories including CBC, chemistry panel, virology/HIV screen, serum pregnancy test (if applicable), and chest x-ray (if applicable) will be obtained or performed at this visit. [redacted] Review of (I/E) criteria and concomitant medications. Female subjects of child-bearing potential must have a negative urine pregnancy test (UPT[redacted] to continue in the study. Limited physical exam including psoriasis assessments (including PASI), full-body photography, quality of life measures, patient reported questionnaires, and study drug injection will be completed. [redacted] Review of interim medical history, AEs and concomitant medications. Limited physical exam including psoriasis assessments (PASI at Weeks 4, 16, 28 and 52), UPT (Weeks 4, 16, 28, 40 and 52, if applicable), quality of life measures, and patient questionnaires will be completed. Full-body photography will be performed at Weeks 16, 28, 52. WPAI

[redacted]

	will be performed at Weeks 16, 28, 40, 52. Study drug injections will occur at Weeks 4, 16, 28, 40 and 52. [redacted]_Review of interim medical history, AEs and concomitant medications. Limited physical exam including psoriasis assessments, UPT (if applicable), quality of life measures, patient questionnaires and end of study procedures will be completed.
Study Measurements	The following assessments will be performed. 1. Quality of life will be measured using the following validated instruments: a. Psychological General Well-Being scale (PGWB) b. Dermatology Life Quality Index (DLQI) 2. Physical parameters, patient satisfaction/happiness with treatment/psoriasis control, and impact on work productivity will also be measured using the following instruments: a. Body Surface Area (BSA) b. Static Physician's Global Assessment (sPGA) c. Psoriasis Area Severity Index (PASI) d. Itch Numerical Rating Scale e. Pain Numerical Rating Scale f. Scaling Numerical Rating Scale g. Tildrakizumab Overall Satisfaction Numerical Rating Scale h. Patient Happiness with Psoriasis Control Numerical Rating Scale i. Treatment Satisfaction Questionnaire for Medication (TSQM) j. Work Productivity and Activity Impairment scale (WPAI-PSO) 3. All AEs will be recorded to assess safety. At each visit after the Baseline Visit, subjects will also be questioned specifically about the status of ongoing AEs.
Study Endpoints	Efficacy Endpoints **Primary** • Improvement in quality of life measured by change from baseline in Psychological General Well-Being scale (PGWB) at Week 28 and Week 52 **Secondary** • Improvement in quality of life measured by change from baseline in Psychological General Well-Being scale (PGWB) over time (weeks 4, 8, 12, 16, 40, 64) ▪ Improvement in quality of life measured by change from baseline in Dermatology Life Quality Index (DLQI) over time (weeks 4, 8, 12, 16, 28, 40, 52, 64) ▪ Proportion of subjects with DLQI score of 0 or 1 at weeks 4, 8, 12, 16, 28, 40, 52, and 64 ▪ Proportion of subjects with DLQI score ≤5 at weeks 4, 8, 12, 16, 28, 40, 52, and 64 ▪ Proportion of subjects with a reduction of ≥ 5 points in DLQI from baseline at weeks 4, 8, 12, 16, 28, 40, 52, and 64 ▪ Efficacy of drug as measured by BSA, sPGA, and/or BSAxPGA over time (weeks 4, 8, 12, 16, 28, 40, 52, 64) ▪ Efficacy of drug as measured by PASI (% of PASI improvement from baseline, absolute PASI) over time (weeks 4,16, 28 and 52)

	▪ Improvement from baseline in itch, pain, and scaling using numerical rating scales over time (weeks 4, 8, 12, 16, 28, 40, 52, 64) ▪ Proportion of patients with itch score of 0, pain score of 0, and scaling score of 0, respectively, at weeks 4, 8, 12, 16, 28, 40, 52, and 64 ▪ Improvement from baseline in work productivity measured by change in Work Productivity and Activity Impairment scale (WPAI-PSO) over time (weeks 16, 28, 40, 52, 64) ▪ Assessment of patient satisfaction with treatment measured with Treatment Satisfaction Questionnaire for Medication (TSQM) over time (weeks 4, 8, 12, 16, 28, 40, 52, 64) ▪ Tildrakizumab overall satisfaction over time (weeks 4, 8, 12, 16, 28, 40, 52, 64) ▪ Patient happiness with psoriasis control over time (weeks 4, 8, 12, 16, 28, 40, 52, 64) Safety Endpoints • AEs
Sample Size Determination	No formal sample size calculations were performed.
Interim Analysis	Planned interim analysis to be performed after all subjects have reached [redacted] All efficacy and safety data up to the date when subjects complete [redacted] (or discontinue prior to completing [redacted] will be included in the interim analysis.
Statistical Methods	All population characteristics and parameters will be described using summary statistics. [redacted] Estimates of the efficacy endpoints of interest will be calculated with [redacted] Adverse events will be presented in data listings and summarized by frequency and severity.



ABBREVIATIONS

AE	Adverse event
BP	Blood pressure
BSA	Body Surface Area
CFR	Code of Federal Regulations
CRF	Case Report Form
DLQI	Dermatology Life Quality Index
FDA	Food and Drug Administration
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICH-GCP	International Conference on Harmonization – Good Clinical Practice
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
NA, N/A	Not applicable
OTC	Over-the-counter
PASI	Psoriasis Area and Severity Index
PFS	Pre-filled Syringe
PP	Per protocol
PT	Preferred Term
PGWB	Physical General Well-Being scale
QoL	Quality of Life
RR	Respiratory Rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
sPGA	Static Physician's Global Assessment
TB	Tuberculosis
TSQM	Treatment Satisfaction Questionnaire for Medication
WOCBP	Women of childbearing potential
WPAI-PSO	Work Productivity and Activity Impairment scale - Psoriasis

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1. INTRODUCTION AND RATIONALE

Psoriasis is a chronic, disfiguring, immune-mediated skin disease, with recent estimates of the global prevalence in adults ranging from 0.51% to 11.43%.[1] Plaque psoriasis is the most common form, affecting approximately 80% to 85% of psoriasis patients, and appears as sharply demarcated, red lesions of variable size usually covered with silver/white scales. Lesions are typically itchy and painful. The severity of plaque psoriasis is moderate-to-severe in an estimated 18% of patients in the U.S. suffering from plaque psoriasis.[2] Biologic agents have greatly enhanced the treatment options of subjects with moderate-to-severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. Currently approved biologics include tumor necrosis factor (TNF) antagonist agents, i.e., etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®), the interleukin [IL]-12 and IL-23p40 antagonist ustekinumab (Stelara®), IL-17 antagonist agents, i.e., secukinumab (Cosentyx®), brodalumab (Siliq®) ixekizumab (Taltz®), and IL-23 antagonists guselkumab (Tremfya®) and tildrakizumab (Ilumya®).

The physical effects of psoriasis are accompanied by a significant and potentially lasting impact on the emotional and psychosocial well-being of patients, and may lead to substantial burden in terms of disability or psychosocial stigmatization.[3,4] Significant loss of productivity and adverse effects on mental well-being result in negative effects not only on individuals but also on society.[5,6] A recent systematic literature review revealed that psoriasis patients suffer from the same deterioration in health-related quality of life as patients with other major medical diseases, including cancer and cardiovascular diseases.[7]

Tildrakizumab, a humanized monoclonal antibody which selectively binds to the p19 subunit of IL-23, was recently approved in the U.S. for patients with moderate-to-severe plaque psoriasis. [redacted]

"Quality of life" refers to the general well-being of individuals and their ability to enjoy normal life activities, encompassing satisfaction with physical and psychological health, social and sexual relationships, and employment. It is important to assess patient-reported quality of life outcomes in addition to physician-assessed physical parameters to truly characterize and assess the burden of psoriasis and response to treatment from the patient's point of view. This study seeks to assess the longer-term impact of tildrakizumab on improvements in HRQoL using multiple assessment scales, as well as assessment of psoriasis symptom control and long-term efficacy and safety, under real world conditions.

Detailed information regarding the safety and tolerability of tildrakizumab can be found in the Investigator's Brochure and package labeling.

2. OBJECTIVES

The primary objective is to demonstrate improvement from baseline in patient quality of life (QOL) after 28 and 52 weeks of treatment with tildrakizumab, under real world conditions, as measured by Psychological General Well-Being scale (PGWB).

Secondary objectives include assessment of patient quality of life as measured by the Dermatology Life Quality Index (DLQI), work productivity and activity impairment, psoriasis symptom control, patient satisfaction, long-term efficacy and safety.

3. STUDY DESIGN

This is a Phase 4 multicenter, uncontrolled open-label study design. There will be a total of 10 study visits at Screening, Baseline, Week 4, Week 8, Week 12, Week 16, Week 28, Week 40, Week 52 and Week 64, with subjects receiving tildrakizumab injections at Week 0, Week 4, Week 16, Week 28, Week 40, and Week 52. The total study duration will be approximately 64 weeks, excluding a screening period.

3.1. Number of Subjects

Approximately 60 subjects will be enrolled into the study at two sites.

3.2. Estimated Duration of Study

For an individual subject, the study duration should be approximately 64 weeks. The duration of the study as a whole will vary based upon the rate of recruitment and completion of subjects.

4. STUDY POPULATION

An individual subject may only be enrolled once in this study. Subjects will be selected from outpatients seeking treatment at the study sites and from individuals recruited by various means including advertisements.

4.1. Inclusion Criteria

To be eligible to enter the study, a subject must meet the following criteria:

1. Subjects are non-immunocompromised males or females 18 years of age or older.
2. Subjects have ≥3% total body surface area plaque psoriasis.
3. Subjects are candidates for phototherapy or systemic therapy.
4. Subject must be diagnosed at least 6 months prior to entering the study.
5. Females must be surgically sterile, postmenopausal for >5 years, or using a highly effective form of birth control (<1% failure rate), for at least 30 days prior to test article exposure, with a negative serum pregnancy test at Screening .

[redacted]

[redacted]

4.2. Exclusion Criteria

A subject is ineligible to enter the study if he/she meets one or more of the following criteria:

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject is younger than 18 years of age.

[redacted]

[redacted]

7. Subjects with uncontrolled mental illness or active suicidal ideations based on mental health questionnaire of choice.

[redacted]

18. Subject is known, or suspected of being unable to comply with the study protocol, in the opinion of the investigator.
19. Subject is currently enrolled in an investigational drug or device study.

[redacted]

4.3. Subject Withdrawal Criteria

Treatment for a subject can be discontinued at any time, if in the opinion of the medical monitor, there are any clinically significant events at any visit that may impact the safety of subject(s). A subject **must** be discontinued from study medication if either of the following occur**:**

- A serious adverse event, drug reaction or complication, or an unacceptable adverse event [redacted] whether attributed to study medication or not, that precludes continuation of treatment with study medication. This includes the development of allergic reactions or the development of other potentially serious drug reactions to medication required by the protocol.

- Pregnancy: A subject who becomes pregnant during the study must discontinue study medication immediately.

In the event that a subject will not receive subsequent treatment (ie, due to safety concerns or refusal), subject will be encouraged to participate in follow-up visits so that safety responses can be monitored. However, subject may withdraw from the study at

any time for any reason. Procedures for handling subjects who withdraw from the study are described in Section 10.2. [redacted]

5. STUDY INTERVENTION

The investigator acknowledges that the test article must be used strictly in accordance with the protocol and only by the investigator and sub-investigators listed on the FDA Form 1572. A sponsor representative will be at the site to inventory drug. The investigator must maintain adequate records documenting the receipt and dispensation of all study supplies. Sponsor will supply forms to record the date drug was received, lot number and a dispensing record to record each subject use.

5.1. Test Article Description

Tildrakizumab is a humanized IgG1/k antibody that specifically binds to the p19 subunit of interleukin-23 (IL-23). Tildrakizumab injection, [redacted] is a sterile, clear to slightly opalescent, colorless to slightly yellow solution. Tildrakizumab 100 mg/mL in 1 mL pre-filled syringes (PFS) will be provided by the Sponsor.

5.2. Formulation, Packaging, Labeling, and Storage

Each 1 mL single-dose PFS contains 100 mg of tildrakizumab formulated in: [redacted]

Test article will be affixed with a clinical label in accordance with regulatory requirements.

Test article must be stored in a secure, limited-access location under the following storage conditions:

- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until the time of use.
- Do not freeze.
- Do not shake.

Site storage conditions should be monitored by the site personnel for adherence to label specifications and reviewed during site visits.

5.3. Treatment Compliance

Test article will be administered by qualified members of the study staff at the investigator's site.

5.4. Dispensing

The study staff should assign the subject numbers in ascending order beginning with the lowest available subject number.

The investigator or qualified designee(s) will dispense test article to subjects who have provided written informed consent and have met the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

See the Schedule of Study Events for a schedule of when test article is to be dispensed to the subjects.

5.5. Test Article Accountability/Supply Records

It is the responsibility of the investigator to ensure that a current record of test article disposition is maintained. Accurate and current accounting of the dispensing of test article will be maintained on an ongoing basis by a member of the site staff; test article dispensed to the site and administered to each subject will be recorded on an Accountabiity Log. Accountability records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received placed in storage area.
- Amount currently in storage area.
- Lot or batch number.
- Dates and initials of the person responsible for each product inventory entry/movement.
- Amount dispensed to each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to sponsor.
- Amount destroyed at study site, if applicable.

Sponsor or designee will provide forms to facilitate inventory control if the staff at the study site does not have an established system that meets these requirements.

The Accountability Log will be verified by the sponsor's monitor. The original Accountability Log will be approved by the investigator and retained at the site and a copy supplied to the sponsor when the study is complete.

Any device administered by site staff in the study which is felt to be defective, should be returned to the sponsor for inspection and follow-up. Specific procedures on the handling

and return of defective devices will be provided in a separate procedures manual for this study.

In the event the investigational products destruction is arranged by the site, copies of the destruction records should be returned to the sponsor.

The sponsor's monitor will instruct the site on the return of all investigational product supplies. A final inventory of the total amount of investigational products received at the study site against the amount used and returned must be recorded in the Accountability Log. Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to government inspection at any time.

6. PRIOR AND CONCOMITANT THERAPY

Current medications and any medications taken in the 12 weeks prior to Visit 1 (Screening) will be recorded as prior/concomitant medications with the corresponding indication. The medications to be recorded include prescription and over-the-counter medications (except vitamins and dietary supplements). All medications taken on a regular basis should be recorded on the CRFs prior to commencing use of the test article.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health. Non-prohibited chronic therapies being used prior to Visit 1 may be continued. Any changes in concomitant therapies during the study must be recorded on the CRFs. The reason for any change in concomitant medications or therapies/procedures should be reported and should reflect either a baseline medical condition documented in the medical history of the CRF or an AE.

6.1. Prohibited Medications or Treatments

Include medications within the following categories:

- Products used within the specified time frames, as specified in Section 4.2.
- Treatment with a biological agent other than test article (including monoclonal antibodies, alefacept)
- Any investigational agents (other than test article)
- New treatments for psoriasis that subject was not using consistently prior to screening

6.2. Allowed Medications or Treatments

- Topical steroids, phototherapy, or other systemic agents at the same strength/dosage that was being used consistently prior to screening, as deemed appropriate by the study investigators
- Medications needed to treat pre-existing medical conditions that are not exclusionary to the study
- Medications necessary to treat adverse events or medical emergencies
- Vitamins, supplements and other over the counter (OTC) medications

The use of concomitant medication/treatment must be recorded on the CRFs and must relate to the documented medical history, prophylaxis, or an adverse event.

7. PROCEDURES

Refer to the Study Schedule of Events for a summary of procedures at each visit.

The timing of each visit is relative to Day 1 (Visit 2), which is defined as baseline.

All visits should be performed within the windows specified in the Study Schedule of Events. Every attempt should be made to have each subject attend each visit as scheduled. However, if a subject is unable to attend a visit within the specified windows, the visit should be scheduled as closely as possible to these windows. If the subject is unable to attend a dosing visit within the specified windows, the investigator or qualified designee should discuss appropriate dosing with the medical monitor (or appropriate designee). A subject should not miss a protocol-specified visit due to scheduling difficulties.

7.1. Visit Activities

[redacted]

Screening procedures should be completed within 30 days prior to the baseline visit (Day 1). The following screening procedures are to be performed:

- Review study information with the subject and obtain written informed consent, including whether they are willing to be contacted by a representative of the sponsor to share their experience, prior to any performing any procedures.
- Obtain demographic information
- Medical history, including psoriasis treatment history.

[redacted]

[redacted]

- Review inclusion and exclusion criteria with the subject to determine eligibility
  - Appropriate medications and washout times will be discussed, including medications prohibited and allowed throughout the study
- Review and record prior medication/therapies [redacted] and concomitant medications/therapies (medications currently used)
- Full physical examination, including psoriasis assessments
  - Height and weight
  - Vital signs: temperature, blood pressure, heart rate, and respiratory rate
  - Comprehensive physical examination
  - Body Surface Area (BSA)
  - Static Physician's Global Assessment (sPGA)
- Clinical Laboratories:
  - Hematology
  - Chemistry

[redacted]

- For females of childbearing potential, obtain the date of the subject's last menstrual period and information on contraceptive use
- If subject meets the inclusion/exclusion criteria, schedule [redacted]
- Update Subject Screening and Enrollment Log

[redacted]

Perform the following:

- Reconfirm inclusion and exclusion criteria
- Quality of Life (QOL) assessments

  - Psychological General Well-Being scale (PGWB)
  - Dermatology Life Quality Index (DLQI)
- Additional subject questionnaires
  - Itch Numerical Rating Scale
  - Pain Numerical Rating Scale
  - Scaling Numerical Rating Scale
  - Patient happiness with psoriasis control
  - Work Productivity and Activity Impairment scale (WPAI-PSO)

- Limited physical examination, including psoriasis assessments.
  - Weight
  - Vital signs: temperature, blood pressure, heart rate, and respiratory rate
  - Body Surface Area (BSA)
  - Static Physician's Global Assessment (sPGA)
  - Psoriasis Area Severity Index (PASI)
- Full-body photography (excluding face)
- Urine Pregnancy Test (if applicable)
  - Urine pregnancy tests must have a minimum sensitivity of 25 mIU β-hCG/ml
- Test article injection
- Record adverse events, concurrent procedures and changes in concomitant medications
- Schedule [redacted]

[redacted]

Perform the following:

- Quality of Life (QOL) assessments
  - Psychological General Well-Being scale (PGWB)
  - Dermatology Life Quality Index (DLQI)
- Additional subject questionnaires
  - Itch Numerical Rating Scale
  - Pain Numerical Rating Scale
  - Scaling Numerical Rating Scale
  - Tildrakizumab Overall Satisfaction Numerical Rating Scale
    - symptom control, safety, etc

  - Patient happiness with psoriasis control
  - Treatment Satisfaction Questionnaire for Medication (TSQM)

- Limited physical examination, including psoriasis assessments.
  - Weight
  - Vital signs: temperature, blood pressure, heart rate, and respiratory rate
  - Body Surface Area (BSA)
  - Static Physician's Global Assessment (sPGA)
  - Psoriasis Area Severity Index (PASI)
- Urine Pregnancy Test (if applicable)
  - Urine pregnancy tests must have a minimum sensitivity of 25 mIU β-hCG/ml
- Test article injection
- Record adverse events, concurrent procedures and changes in concomitant medications
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[redacted]

Perform the following:

- Quality of Life (QOL) assessments
  - Psychological General Well-Being scale (PGWB)
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- Additional subject questionnaires
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  - Pain Numerical Rating Scale
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- Limited physical examination, including psoriasis assessments.
  - Weight
  - Vital signs: temperature, blood pressure, heart rate, and respiratory rate
  - Body Surface Area (BSA)

- Static Physician's Global Assessment (sPGA)

- Record adverse events, concurrent procedures and changes in concomitant medications
- Schedule [redacted]

[redacted]

Perform the following:

- Quality of Life (QOL) assessments
  - Psychological General Well-Being scale (PGWB)
  - Dermatology Life Quality Index (DLQI)
- Additional subject questionnaires
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  - Vital signs: temperature, blood pressure, heart rate, and respiratory rate
  - Body Surface Area (BSA)
  - Static Physician's Global Assessment (sPGA)
  -
- Record adverse events, concurrent procedures and changes in concomitant medications
- Schedule [redacted]

[redacted]

Perform the following:

- Quality of Life (QOL) assessments
  - Psychological General Well-Being scale (PGWB)
  - Dermatology Life Quality Index (DLQI)

- Additional subject questionnaires
    - Itch Numerical Rating Scale
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- Test article injection
- Record adverse events, concurrent procedures and changes in concomitant medications
- Schedule [redacted]

[redacted]

Perform the following:

- Quality of Life (QOL) assessments
    - Psychological General Well-Being scale (PGWB)
    - Dermatology Life Quality Index (DLQI)
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    - Itch Numerical Rating Scale
    - Pain Numerical Rating Scale
    - Scaling Numerical Rating Scale

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    - Body Surface Area (BSA)
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    - Psoriasis Area Severity Index (PASI)
- Full-body photography (excluding face)
- Urine Pregnancy Test (if applicable)
    - Urine pregnancy tests must have a minimum sensitivity of 25 mIU β-hCG/ml
    -
- Test article injection
- Record adverse events, concurrent procedures and changes in concomitant medications
- Schedule [redacted]

[redacted]

Perform the following:

- Quality of Life (QOL) assessments
    - Psychological General Well-Being scale (PGWB)
    - Dermatology Life Quality Index (DLQI)
- Additional subject questionnaires
    - Itch Numerical Rating Scale
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  - Urine pregnancy tests must have a minimum sensitivity of 25 mIU β-hCG/ml
- Test article injection
- Record adverse events, concurrent procedures and changes in concomitant medications
- Schedule [redacted]

[redacted]

Perform the following:

- Quality of Life (QOL) assessments
  - Psychological General Well-Being scale (PGWB)
  - Dermatology Life Quality Index (DLQI)
- Additional subject questionnaires
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  - Scaling Numerical Rating Scale
  - Tildrakizumab Overall Satisfaction Numerical Rating Scale
    - symptom control, safety, etc
  - Patient happiness with psoriasis control
  - Treatment Satisfaction Questionnaire for Medication (TSQM)
  - Work Productivity and Activity Impairment scale (WPAI-PSO)

- Limited physical examination, including psoriasis assessments.
  - Weight
  - Vital signs: temperature, blood pressure, heart rate, and respiratory rate
  - Body Surface Area (BSA)
  - Static Physician's Global Assessment (sPGA)
  - Psoriasis Area Severity Index (PASI)
- Full-body photography (excluding face)
- Urine Pregnancy Test (if applicable)

- Urine pregnancy tests must have a minimum sensitivity of 25 mIU β-hCG/ml

- Test article injection
- Record adverse events, concurrent procedures and changes in concomitant medications

[redacted]

Perform the following:

- Quality of Life (QOL) assessments
  - Psychological General Well-Being scale (PGWB)
  - Dermatology Life Quality Index (DLQI)
- Additional subject questionnaires
  - Itch Numerical Rating Scale
  - Pain Numerical Rating Scale
  - Scaling Numerical Rating Scale
  - Tildrakizumab Overall Satisfaction Numerical Rating Scale
    - symptom control, safety, etc
  - Patient happiness with psoriasis control
  - Treatment Satisfaction Questionnaire for Medication (TSQM)
  - Work Productivity and Activity Impairment scale (WPAI-PSO)
- Limited physical examination, including psoriasis assessments.
  - Weight
  - Vital signs: temperature, blood pressure, heart rate, and respiratory rate
  - Body Surface Area (BSA)
  - Static Physician's Global Assessment (sPGA)
- Urine Pregnancy Test (if applicable)
  - Urine pregnancy tests must have a minimum sensitivity of 25 mIU β-hCG/ml
- Record adverse events, concurrent procedures and changes in concomitant medications
- Complete EOS form

8. CLINICAL EVALUATIONS/PRO ASSESSMENTS

The following clinical evaluations will be performed according to the Schedule of Study Events and Section 7.1. The same investigator should complete the evaluations for a

given subject throughout the study. If this becomes impossible a sub-investigator with overlapping experience with the subject and the study should complete the evaluations.

8.1. Body Surface Area (BSA)

The percent BSA affected with psoriasis will be estimated at each study visit. The investigator may use the estimate that 1% BSA is equivalent to the area of the subject's closed hand (palm with fingers held together).

8.2. Static Physician's Global Assessment (sPGA)

The sPGA, previously described by Chow et al[10], is used to determine the overall severity of psoriasis lesions at a given time point. This evaluation is not a comparison with the sPGA at any other visit. [redacted] Each attribute will be averaged over the subject's entire body. [redacted]

8.3. Psoriasis Area Severity Index (PASI)

The PASI is a quantitative rating scale for measuring the severity of psoriatic lesions based on area coverage and plaque appearance, which has been shown to have a significant degree of concordance among evaluators.[11] PASI analyzes the four regions of the body (head, trunk, upper and lower limbs) [redacted] and BSA affected. [redacted]

8.4. Itch Numerical Rating Scale (I-NRS)

The I-NRS is a simple, [redacted] self-administered numeric rating scale [redacted] At each visit, subjects indicate itch severity by circling the integer that best describes the worst level of itching due to psoriasis in the past 24 hours on an [redacted].

Figure 8-1 I-NRS Questionnaire

[redacted]

8.5. Pain Numerical Rating Scale (P-NRS)

The P-NRS is a simple [redacted] self-administered numeric rating scale [redacted] that is administered at each visit. Subjects indicate skin pain severity by circling the integer that best describes the worst level of skin pain due to psoriasis in the past 24 hours on an [redacted]

[redacted]

8.6. Scaling Numerical Rating Scale (S-NRS)

The S-NRS is a simple, [redacted] self-administered numeric rating scale [redacted] that is administered at each visit. Subjects indicate scaling severity by circling the integer that best describes the worst level of scaling due to psoriasis in the past 24 hours on an [redacted] scale [redacted]

[redacted]

8.7. Psychological General Well-Being Index (PGWB)

The PGWB is a self-administered validated psychometric instrument that measures a person's emotional well-being.[12] It is specifically designed to be suitable for assessing psychological well being in the general medical population as opposed to a psychiatric population. The 22 questions of the PGWB [redacted] is graded on a Likert scale, which is commonly used in psychometric questionnaires where the answers range from strongly agree to strongly disagree with gradations in between. Total scores range from 0 to 110, with higher scores indicating better psychological well being. This instrument has been validated and used in many countries on large samples of the general population and on various subsets of medical patients. [redacted]

8.8. Dermatology Life Quality Index (DLQI)

The DLQI is a self-administered and user-friendly validated questionnaire used to measure the health-related quality of life of adult patients suffering from a skin disease.[13] It consists of [redacted] questions concerning patients' perception of the impact of skin diseases on different aspects of their health related quality of life over the last week. It has been validated for adult dermatology patients aged 16 years and older. [redacted] higher scores mean greater impairment of patient's QoL. [redacted]

8.9. Work Productivity and Activity Impairment Scale (WPAI-PSO)

The WPAI is a validated, subject-reported quantitative assessment of the amount of absenteeism, presenteeism and daily activity impairment attributable to general health or a specific health problem.[14] The WPAI has been validated to specifically quantify work impairments for numerous diseases and the WPAI:PSO was created specifically for administering to patients with psoriasis.[15] WPAI surveys were analyzed based on

published algorithms to determine the following: current employment status, absenteeism [redacted] presenteeism [redacted] total activity impairment [redacted] and total work productivity impairment [redacted] higher scores representing greater impairment (worse outcomes). [redacted]

8.10. Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM is a general measure of treatment satisfaction with medication, suitable for use across a wide variety of medication types and illness conditions. The [redacted] TSQM Version 1.4 is a reliable and valid instrument to assess patients' satisfaction with medication, providing scores on four scales – side effects, effectiveness, convenience and global satisfaction. [redacted]

8.11. Tildrakizumab Overall Satisfaction

The Tildrakizumab Overall Satisfaction Scale is a simple, [redacted] self-administered numeric rating scale [redacted] that is administered at each visit starting at [redacted] Subjects indicate their overall satisfaction with the use of tildrakizumab as well as on specific areas by circling the integer that best describes their experience on an [redacted] scale [redacted] pecific areas assessed are:

- Improvement in symptoms
- Speed of symptom improvement
- Frequency of taking the medicine
- Side effects experienced, if any

8.12. Patient Happiness with Psoriasis Control

The Patient Happiness with Psoriasis Control assessment is a simple, [redacted] self-administered numeric rating scale [redacted] that is administered at each visit. Subjects indicate their overall happiness with psoriasis control by circling the integer that best describes their experience on an [redacted]

8.13. Full-Body Photography (excluding face)

Full-body photographs will be taken on consenting subjects. Clinical photographs should be standardized using a solid color background and consistent subject positioning and lighting. Approximately six views should be taken; full front, full back and four half-body views, ensuring that all non-head areas affected by psoriasis are

captured. Subjects who refuse to undergo full-body photography may still be enrolled in the study.

9. Laboratory Tests

9.1. Pregnancy Tests

A serum pregnancy test must be performed on all female subjects of child-bearing potential at Visit 1. A UPT will be performed in women of childbearing potential at all visits where study article is administered. The UPT used must have a minimum sensitivity of 25mIU of β-hCG/mL of urine. Please see Schedule of Study Events for all subsequent UPTs. The investigator will report the UPT results on the CRFs, in the subject's medical records and in any independent records maintained at the study site. Subjects with a positive pregnancy test at Visit 1 or prior to the first dose of test article will not be allowed to enter the study (screen failure). Subjects with a positive pregnancy test any time after the first dose of test article will not receive further test article; however subjects should continue with non-treatment follow-up visits. All pregnancies should be immediately reported to the medical monitor and followed through to resolution (i.e., delivery, miscarriage, or abortion). The report should be submitted within the 24 hours of knowledge.

9.2. Laboratory Safety Tests

Laboratory tests for hematology, blood chemistry, and virology/HIV [redacted] Blood samples for laboratory tests are to be taken prior to first administration of test article and should be performed according to standard laboratory procedures. Followup labs for chemistry, blood count and virology beyond screening can be done at the clinical judgment of the investigator.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
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[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	

10. END OF STUDY (EOS) CRITERIA

At the end of each subject's participation in the study, the investigator will complete an End of Study form for all completed and discontinued subjects.

10.1. Completion of the Study

Subjects who complete the treatment as specified in the protocol and who complete the End of Study evaluations will be considered to have completed the study.

10.2. Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

• Whenever the subject decides it is in the subject's best interest to withdraw. NOTE: if the subject decides it is in the subject's best interest to withdraw due to an AE then it should be classified as withdrawal due to an AE.

• Whenever the investigator decides it is in the subject's best interest to be withdrawn

• AEs

• Worsening of condition or treatment failure (in the opinion of the investigator)

• Intercurrent illness which may, in the investigator's opinion, significantly affect assessment of clinical status

• Noncompliance

• Lost to follow-up

• Sponsor administrative reasons

If a subject withdraws prematurely during the treatment period, complete the CRF for the appropriate visit, then complete the End of Study CRFs.

10.3. Screen Failures

If a subject is a screen failure at Visit 1, complete the Screen Failure CRF.

11. SAFETY

11.1. Adverse Events (AE)

An adverse event (**AE**) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug without any judgment of causality.

Information on the medical condition of subjects should begin following the subject's written consent to participate in the study and a medical history should be taken at screening. During any wash out and baseline periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and is unanticipated; where in such cases, the event should be recorded as an adverse event and reported to the Institutional Review Board (IRB) as an "unanticipated problem" in accordance with local procedures. Other changes in subject health information becomes AE data when the subject begins dosing with the test article and therefore AE data should be collected from the date of the first dose of test article. These data are considered treatment-emergent AEs.

Timely and complete reporting of all AEs assists the Sponsor in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of study subjects;

2) a greater understanding of the overall safety profile of the test article;

3) recognition of dose-related test article toxicity;

4) appropriate modification of study protocols;

5) improvements in study design or procedures; and

6) adherence to worldwide regulatory requirements.

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. The investigator will instruct the subject to report any adverse events that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall condition since the previous visit. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms.

All AEs must be completely recorded on the AE CRF and include the following:

- **Date of onset**
- **Location of the event – specify whether within affected region**
- The **Severity** of the event. Record the maximum intensity taking into account the possible range of the intensity of the event, using the following definitions:

SEVERITY	
Mild	Adverse event noticeable by the subject but did not interfere in a significant manner with the subject's normal functioning; remedial therapy may have been given.
Moderate	The adverse event was sufficiently intense to produce some impairment of functioning; remedial therapy may have been given.
Severe	The adverse event produced a significant impairment of functioning or incapacitation; therapy was needed.

- Categorize the Relationship to Study Treatment of the AE, as defined below:

RELATIONSHIP	
Not Related:	Concomitant illness, caused by other drug, procedure, accident or event with no reasonable association with treatment.
Unlikely:	An event that does not follow a reasonable temporal association sequence from administration of the test article; that does not follow a known or expected response pattern to the test article, or most likely was caused by the subject's clinical state, other drug, procedure, or other causes, because of their known effects.
Possibly:	An event that follows a reasonable temporal sequence from administration of the test article; follows a known or expected response pattern to the test article; but may have been produced by the subject's clinical state or by other drugs or procedures administered to the subject, or by other causes.
Probably:	An event that follows a reasonable temporal sequence from administration of test article; follows a known or expected response pattern to the test article; is confirmed by improvement on stopping or reducing the dosage; cannot be reasonably explained by the known characteristics of the subject's clinical state or other drugs, procedures or other causes.
Definite:	An event that follows a reasonable temporal sequence from administration of test article; follows a known or expected response pattern to the test article; is confirmed by improvement on stopping or reducing the dosage, and reappearance of the event on repeat exposure (rechallenge).

- Determine the **Action Taken with Study Treatment** due to the AE using the definitions below:

[redacted]

[redacted]

[redacted]

[redacted]

Subjects experiencing AEs that cause interruption or discontinuation of test article, or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. If possible, report the outcome of any AE that caused permanent discontinuation or that was present at the end of the study particularly if the AE is considered by the investigator to be treatment-related (i.e., definitely, probably, or possibly related to test article).

- Determine if the event is considered **Serious** based on the definitions in Section 11.2.
- Record whether the event caused Study Discontinuation.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

A **suspected adverse reaction** is any adverse event for which there is a reasonable possibility that the drug caused the event.

For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.2. Serious Adverse Events (SAE)

An assessment of the **seriousness** and causality of the event will be made by the investigator, the medical monitor and the Sponsor's pharmacovigilance (PV) department. The investigator is to complete a special form provided by the Sponsor in the case of a SAE; expeditious handling is required to comply with regulatory requirements. SAEs will also be recorded on the AE CRF.

An **SAE** is classified as any untoward medical occurrence which at any dose

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct life functions
- Is a congenital anomaly/ birth defect
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical judgement, may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These should also be considered serious.

Events NOT considered to be serious adverse events are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen, and
- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

The investigator should take appropriate diagnostic and therapeutic measures to minimize the risk to the subject. Where appropriate, the investigator should take diagnostic measures to collect evidence for clarification of the relationship between the SAE and the investigational product.

Adverse events classified as "serious" by either the investigator or the Sponsor require expeditious handling and reporting to the Sponsor to comply with regulatory requirements. **All serious AEs, whether related or unrelated to test article, must be immediately reported no later than 24 hours of receipt by telephone to the Medical Monitor, the Sponsor's PV department via email [redacted] and, in the event that the Medical Monitor is unavailable, to the Project Manager listed on the first page of the protocol.** Written notification of all SAEs should be sent

to the Medical Monitor/Project Manager and the Sponsor's PV department by email or confirmed facsimile transmission. These include those SAEs listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of a SAE (regardless of its relationship to test article) that occurs within 30 days after stopping the test article, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to the Sponsor, if available.

As required, the Sponsor will notify participating investigators of all suspected adverse reactions that are serious and unexpected. This notification will be in the form of an IND safety report of potential serious risks as soon as possible but no later than 15 calendar days after the Sponsor determines that the information is "reportable" according to the criteria listed in 21 CFR Section 312.32. These are:

i) Serious and unexpected suspected adverse reactions,

ii) Findings from other studies including epidemiological studies, pooled analyses or other clinical studies that suggest a significant risk in humans exposed to the test articles,

iii) Findings from animal or in vitro tests that suggest a significant risk to humans exposed to the test articles, or reports of significant organ toxicity at or near the expected human exposure, and

iv) Clinically important increases in the rate of occurrence of serious suspected adverse reactions.

Upon receiving such notices, the investigator must review and retain the notice with the Investigator Brochure and immediately submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of safety updates by the investigator to Health Authorities should be handled according to local regulations.

The IRB may require the investigator to report serious adverse events that are possibly related to the study drug or all serious adverse events regardless of relatedness. The IRB requirements should be reviewed carefully. The investigator is responsible to notify the IRB of specific adverse event information as specified in the IRB approval.

11.3. Pregnancy

Before enrolling women of childbearing potential in this clinical study, investigators must review the following information about study participation for women:

- Informed consent requirements
- Contraceptives in current use
- Drug interactions with hormonal contraceptives
- Guidelines for the follow-up of a reported pregnancy in this clinical study.

All female subjects of child-bearing potential must agree to use a highly effective form of birth control (See Section 4) during the course of the study in a manner such that risk of failure is minimized. Prior to study enrollment, all female subjects of child-bearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Following review of this information and appropriate subject counseling, the investigator or designee and the subject must sign the informed consent.

If pregnancy is confirmed during screening, the subject must not receive test article and must not be enrolled in the study. All females of childbearing potential enrolling into the study must have pregnancy testing prior to each administration of test article. The test article administration must be withheld until the result of pregnancy testing is known. During the study, all female subjects should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the subject must not receive further study therapy; however every effort should be made to retain the subject in the study and complete all follow-up visits. At a minimum, the subject must be followed for safety.

The Investigator must immediately notify the Medical Monitor and IRB of any pregnancy associated with the study therapy, maintain careful source documentation and record the event on the appropriate CRF and pregnancy surveillance form. Protocol-required procedures (except for administration of test article) for pregnant subjects must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate follow-up procedures including counseling of the subject by the investigator and her obstetrician should be considered, if appropriate. In addition, the Investigator must report any follow-up information to the Medical Monitor and the IRB regarding the course of the pregnancy, including perinatal and neonatal outcome on the pregnancy surveillance form provided. Although pregnancy itself is not an adverse event, any complications during pregnancy should be recorded as AEs (or SAEs – if they fulfill the SAE criteria). Abortion, whether accidental, therapeutic or spontaneous should be reported as a SAE. Infants should be followed for a minimum of 8 weeks or as required by the IRB or local law, whichever is longer. Any congenital anomaly/birth defect in a

child born to a subject exposed to test article should be recorded as a SAE and details documented on the pregnancy surveillance form.

12. STATISTICAL CONSIDERATIONS

12.1. General Considerations for Data Analysis

The methodology presented below is a summary of the more detailed analysis plan that will be presented in the Statistical Analysis Plan (SAP). The SAP will be finalized before the database is locked. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

It is planned that the data from both centers that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

All statistical analyses will be performed using SAS statistical software.

12.2. Sample Size Determination

No formal sample size calculations were performed. The sample size of 60 subjects was selected to provide adequate estimates of probably events in the population.

12.3. Analysis Populations

Efficacy will be investigated in 2 populations. The PP population will comprise all subjects who are enrolled and receive all doses of the study medication, have no major study protocol violations and do not use any prohibited medications during the study period. The ITT population will comprise all subjects who are enrolled and assigned to receive the study medication. The safety population will comprise all subjects who are enrolled and receive at least one dose of the study medication.

[redacted]

12.4. Statistical Methods

All population characteristics and parameters will be described using summary statistics. Categorical variables will be summarized using frequency counts and percentages. Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) will be calculated for each continuous variable. Estimates of the efficacy endpoints of interest will be calculated with [redacted] wherever possible. [redacted]

Adverse events will be presented in data listings and summarized by frequency and severity.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Compliance with Good Clinical Research Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The investigator and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent documents, recruitment advertisements and any amendments to these items will have IRB approval prior to study initiation. Voluntary informed consent will be given by every subject prior to the initiation of any study-related procedures. Subjects must provide written consent. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

13.2. Institutional Review Board and Informed Consent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the Investigator Brochure, prescribing information, information to be provided to subjects and any updates. The investigator will submit documentation of the IRB approval to Sponsor or designee.

The IRB-approved consent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The investigator/designee will explain the study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The investigator must provide the subject with a copy of the consent form in a language the subject understands.

The investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

13.3. Protocol Compliance

The IRB-approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

13.4. Protocol Revisions

The Sponsor must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to Sponsor or designee.

New or altered consent forms required by the IRB due to a protocol change must be signed by all subjects for those subjects currently enrolled in the study and must be used for any subsequent subject enrollment.

13.5. Study Monitoring

Representatives of the Sponsor or designee must be allowed to visit study site, to review study records and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff and to verify that the investigator, study staff and facilities remain acceptable for the conduct of the study. Key study personnel must be available to assist the study monitor during these visits.

Representatives of government regulatory authorities may also evaluate the study records, source documents, investigator, study staff and facilities.

The investigator should immediately notify Sponsor or designee of any audits of this study by any regulatory agency, and must promptly provide copies of any audit reports.

13.6. Data Collection Form Requirements

The Sponsor will provide the site with data collection forms, be they Case Report Forms (CRF), either in paper format or electronic Case Report Forms (eCRF); diaries; questionnaires; Electronic Data Capture (EDC) screens; or other appropriate data collection forms as the study requires. The investigator is to provide subject data according to the Sponsor's instructions, in the designated data collection form, compliant with GCP practices. The Sponsor will also provide the site with instructions for assisting other parties - such as a central laboratory - to collect data, if applicable. As instructed by the Sponsor, a designated central laboratory may collect data in a database and provide the completed database to sponsor. All data collection forms and the databases from the study are the exclusive property of sponsor.

The investigator must maintain records and data during the study in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the study site. Any records or documents used as the source of information (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator will ensure that there is sufficient time, staff, and facilities available for the duration of the study to conduct and record the study as described in the protocol and according to all applicable guidance, laws, and regulations.

All data collection forms (e.g., CRFs, diaries; questionnaires; EDC screens), electronic database entries, etc., should be completed as soon as possible after the evaluation has occurred. All dates appearing on the sponsor's subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. Qualified designees must be listed on the Delegation of Responsibilities Log with responsibility for CRF completion. The investigator or physician sub-investigator must electronically sign and date each subject's CRF.

13.7. Reports to Institutional Review Board

The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

13.8. Quality Assurance Audits

Representatives of the Sponsor or a third party selected by the Sponsor may conduct a quality assurance audit of this study. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The investigator must notify TI in the event of a FDA site audit.

13.9. Records Retention

The investigator must maintain all study records (including test article disposition, informed consents, CRFs/data clarification forms, source documents, correspondence, regulatory documents, contracts, etc.) for a period of at least five years after the study close-out monitoring visit. Records may be maintained in archive at the study site or designated off-site archive. The Sponsor will notify the investigator/Institution in writing when the related records are no longer needed.

The investigator must contact the Sponsor or designee prior to destroying any records associated with this study.

If the investigator withdraws from the study the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to Sponsor.

13.10. Record Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring by the Sponsor or designee, the FDA or other regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

14. PUBLICATION POLICY

The data collected during this study are the property of the Sponsor. A study site may not publish results of this study until after a coordinated multicenter publication has been submitted by the Sponsor for publication in a peer review journal. Thereafter, the study site may obtain written permission from the Sponsor to study data for presentation or publication provided that the Sponsor has the opportunity to review and comment on the proposed publication before it is submitted to a scientific congress or peer review journal. The study site agrees to provide a final draft of the publication to the Sponsor no less than 45 days prior to submission for publication or presentation for review (including, without limitation, slides, abstracts, posters, manuscripts, and other publication types) that report any results of the study. The Sponsor shall have the right to review and comment on the data analysis with regard to the following concerns:

- The accuracy of the information contained in the publication;
- To ensure the publication is fairly balanced and in compliance with regulatory authorities
- Proprietary information that is protected by the following provisions: no publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, the Sponsor shall promptly identify such subject matter to the study site and study site agrees to cease publication submission until Sponsor has the opportunity to file a patent application covering such subject matter.

Publications from this study must be developed and submitted in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and Good Publication Practices.

15. FINANCING AND INSURANCE

The Sponsor shall carry an insurance policy to cover compensation of subjects' health injuries arising from the study. If a subject incurs a study-related injury, the subject may be treated (and other necessary measures taken) at the study site and/or another medical institution. If it is necessary to compensate for the treatment, the Sponsor will cover the cost. The Sponsor shall not impose on the subject the burden of proving the causal relation between the study and the injury.
If any of the following is confirmed, the Sponsor may refuse or restrict the payment of the compensation:

- A serious GCP or protocol deviation by the Investigator or Sub-Investigator (except deviation medically necessary to avoid an immediate hazard to the study subjects)
- Intentional act or negligence on the part of the Investigator or Sub-Investigator or malpractice thereby
- Injury caused by unlawful act or delinquency of a third party
- Injury caused by intentional act or negligence of the subject.

If compensation becomes necessary for a study-related injury, the site will promptly notify the Sponsor and will co-operate with the Sponsor and its insurer (or their legal representatives) in their handling thereof.

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17. APPENDIX A: ELEMENTS OF INFORMED CONSENT

a. Basic elements of informed consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and who to contact in the event of a research related injury to the subject.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
9. A statement that a description of the trial will be available on www.ClinicalTrials.gov, as required by U.S. Law.

b. Additional elements of informed consent.

When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is, or may become, pregnant) which are currently unforeseeable.

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State or Local laws which require additional information to be disclosed for informed consent to be legally effective.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State or Local law.

DOCUMENTATION OF INFORMED CONSENT (21CFR50.27)

Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

Except as provided in 56.109(c), the consent form may be either of the following:

A written consent document that embodies the elements of informed consent required by 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

A *short form* written consent document stating that the elements of informed consent required by 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 2 Static Physician's Global Assessment Score (averaged over all lesions)

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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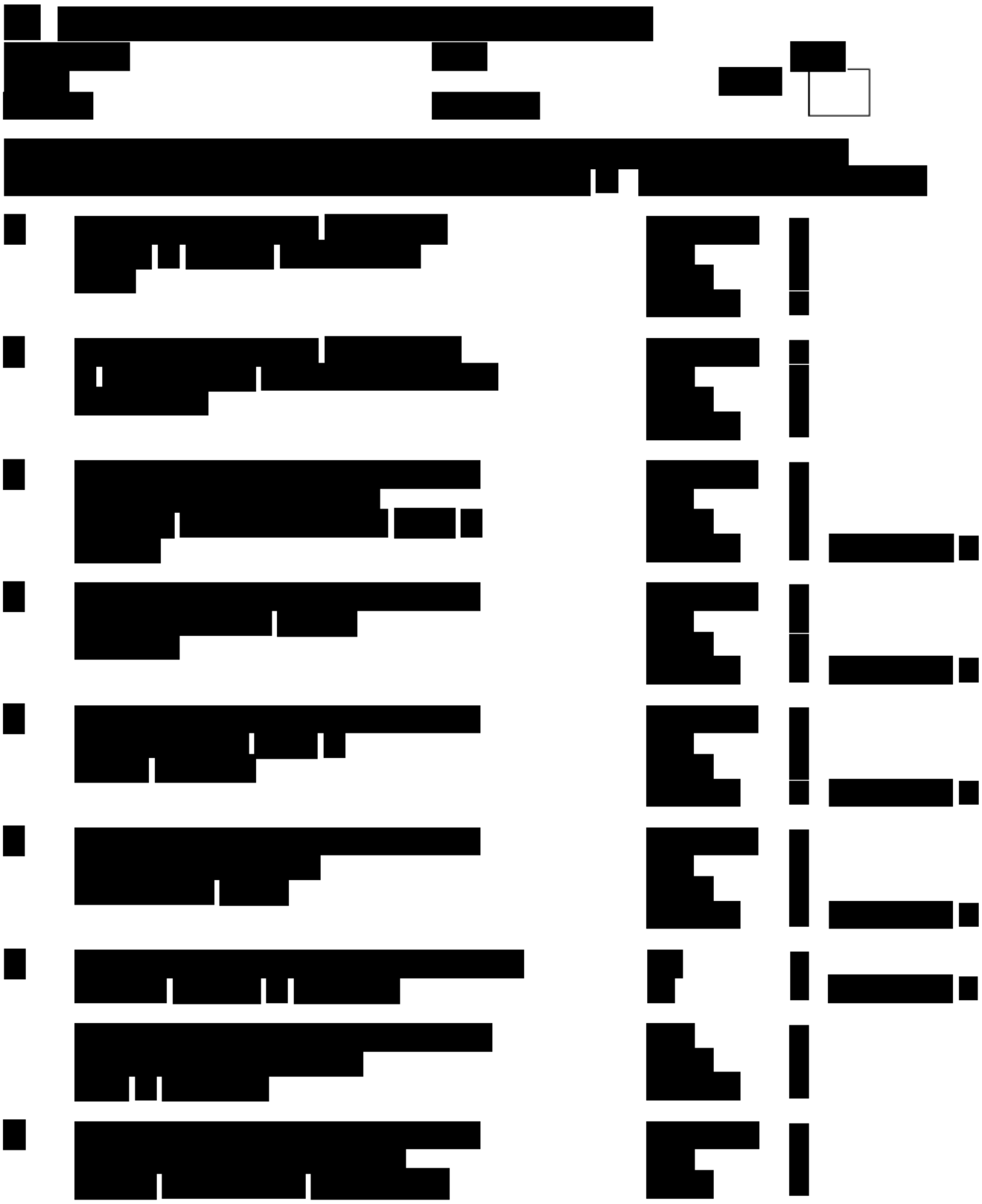

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