A PHASE 1b, OPEN-LABEL, SINGLE-ARM, DOSE-SELECTION, PROOF-OF-CONCEPT STUDY TO ASSESS THE SAFETY AND EFFICACY OF A NOVEL HSP90 INHIBITOR (CUDC-305) IN THE TREATMENT OF MODERATE TO SEVERE PLAQUE PSORIASIS

PROTOCOL CUDC 305

FINAL

VERSION 4.0

22 June 2018

Sponsor: Dr. Anne Bregnhøj
Department of Dermatology
Aarhus University Hospital
P.P. Orums Gade 11
DK-8000 Aarhus C
Denmark

Confidential and proprietary. Permission should be obtained before any reproduction.

TABLE OF CONTENTS

Confidential and proprietary. Permission should be obtained before any reproduction.

Confidential and proprietary. Permission should be obtained before any reproduction.

Confidential and proprietary. Permission should be obtained before any reproduction.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments and provide the necessary assurances that this trial will be conducted according to local legal and regulatory requirements, and International Council for Harmonisation guidelines.

Sponsor:

Name (printed)

Title

Signature Date (DD-MMM-YYYY)

Director Scientific Affairs – Innovaderm:

Name (printed)

Title

Signature Date (DD-MMM-YYYY)

Study Statistician:

Name (printed)

Title

Signature Date (DD-MMM-YYYY)

Confidential and proprietary. Permission should be obtained before any reproduction.

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____
(DD-MMM-YYYY)

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board/Independent Ethics Committee procedures, instructions from Innovaderm Research representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and local regulations governing the conduct of clinical studies.

Confidential and proprietary. Permission should be obtained before any reproduction.

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
anti-HBc	anti–hepatitis B core antibodies
AST	aspartate aminotransferase
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
β-hCG	β-human chorionic gonadotropin
BCG	Bacillus Calmette–Guérin
BMI	body mass index
Bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CK	creatine kinase
CRF	case report form
CYP450	cytochrome P450
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
ET	early termination (visit)
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HBsAg	hepatitis B surface antigens
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IL	interleukin
IRB	institutional review board
ITT	intent-to-treat (population)
LDH	lactate dehydrogenase
LMW	low molecular weight
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MPV	mean platelet volume
MTD	maximum tolerated dose
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index

Confidential and proprietary. Permission should be obtained before any reproduction.

PBMC	peripheral blood mononuclear cell
PGA	Physician's Global Assessment
PK	pharmacokinetics
PP	per-protocol (population)
PPD	purified protein derivative
RBC	red blood cell (count)
REB	research ethics board
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAF	safety (population)
TB	tuberculosis
TEAE	treatment-emergent adverse events
TNF	tumor necrosis factor
ULN	Upper Limit of Normal
WBC	white blood cell (count)

Confidential and proprietary. Permission should be obtained before any reproduction.

SUMMARY

Title: A Phase 1b, open-label, singlecenter, single-arm, dose-selection, proof-of-concept study to assess the safety and efficacy of a novel HSP90 inhibitor (CUDC-305) in the treatment of moderate to severe plaque psoriasis

Phase: 1b

Population: Approximately 12 and not exceeding 16 male or female subjects aged 18 years or older with moderate to severe plaque psoriasis will be included in this study.

Number of Sites: One center in Denmark will participate in this study.

Study Duration: Subject participation will be approximately 20 weeks, involving a 4-week screening phase, a 12-week treatment phase, and a 4-week observational follow-up phase to assess for psoriasis relapse and flare.

Objectives:

Primary:

- To determine the optimal efficacious dose-range of CUDC-305 in the treatment of moderate to severe plaque psoriasis in a Phase 1b proof-of-concept study

Secondary:

- To evaluate the safety and tolerability of CUDC-305 in the treatment of moderate to severe plaque psoriasis
- To investigate changes in skin and blood biomarkers

Endpoints:

Primary Efficacy Endpoint:

- Change from baseline in Psoriasis Area and Severity Index (PASI) score at Week 12

Secondary Efficacy Endpoints:

- Proportion of subjects with Physician's Global Assessment (PGA) of clear or almost clear at Weeks 2, 4, 8, 12, and 16
- Change and percent change from baseline in body surface area (BSA) covered with plaque psoriasis at Weeks 2, 4, 8, 12, and 16
- Change and percent change from baseline in BSA multiplied by the PGA at Weeks 2, 4, 8, 12, and 16

Confidential and proprietary. Permission should be obtained before any reproduction.

- Proportion of subjects achieving 50%, 75%, and 90% reduction from baseline in PASI at Weeks 2, 4, 8, 12, and 16
- Change and percent change from baseline in PASI scores at Weeks 2, 4, 8, and 16
- Percent change from baseline in PASI scores at Week 12
- Change from baseline in pruritus Numeric Rating Scale (NRS) at Weeks 2, 4, 8, 12, and 16
- Change from baseline in the Dermatology Life Quality Index (DLQI) total score at Weeks 4, 8, 12, and 16
- Change from baseline in skin and blood biomarkers at Weeks 4, 8, and 12

Secondary Safety Endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of related TEAEs

Overall Study Design:

This is a 12-week treatment, singlecenter, open-label, single-arm, dose-selection, proof-of-concept study to determine a dosage of CUDC-305 that is tolerable and demonstrates preliminary efficacy for use in future efficacy Phase 2 trials.

Eligible subjects will be sequentially assigned to one of the four cohorts (approximately n = 4 per cohort) receiving ascending or descending doses of CUDC-305. The first cohort will be administered a starting oral dose of 250 mg/d for 12 weeks, which is believed to be the target effective dose for treatment of psoriasis. The dose regimen to be administered to the subsequent cohort will be decided after reviewing the safety and efficacy data of the first four subjects completing the treatment period (12 weeks) in the current cohort. A safety meeting will take place to review the available data prior to deciding the next dose and then initiating dosing of the subsequent cohort. The doses that will be evaluated in this study range between 100 mg and 1000 mg and may include: 100 mg, 250 mg, 500 mg, 800 mg, or 1000 mg orally once daily.

The sponsor and principal investigator(s) will jointly evaluate the safety and tolerability of CUDC-305 at the safety meeting, and intolerability will be determined by taking into account all information from adverse events (AEs), vital signs, physical examination findings, laboratory abnormalities, and electrocardiogram (ECG) findings. The study may be stopped permanently or interrupted at any time for safety reasons.

PASI, PGA, BSA, pruritus NRS, and DLQI will be performed to assess efficacy. Safety will be assessed with the vital signs, physical examination, clinical laboratory tests, ECG, and collection of AEs.

Skin biopsies will be collected from nonlesional and lesional skin for immunohistochemistry and gene expression analysis.

Medical photographs of the target lesion will also be performed at each study visit (except the screening visit).

Confidential and proprietary. Permission should be obtained before any reproduction.

Inclusion Criteria:

Subjects will be eligible to be enrolled in the study if they meet all of the following criteria at the screening and baseline (Day 0) visits, unless specified otherwise:

1. Men or women aged 18 years or older at the time of consent.
2. Subject has a history of plaque psoriasis for at least 6 months prior to the screening visit.
3. Subject has stable psoriasis conditions for at least 3 months before screening, according to subject.
4. Subject has plaque psoriasis covering ≥3% of his total BSA at baseline (Day 0).
5. Subject has a PASI score of ≥6 at baseline (Day 0).
6. Subject has a PGA score of ≥3 at baseline (Day 0).
7. Subject has a body mass index (BMI) ≤40 kg/m^2.
8. Subject is a candidate for phototherapy or systemic treatement of psoriasis (either naïve or has a history of previous treatment).
9. Subjects (women and men) involved in any sexual intercourse that could lead to pregnancy must agree to use an effective contraceptive method from at least 4 weeks before baseline (Day 0) until at least 4 weeks after the last study product administration for the duration of the study. Effective contraceptive methods are: systemic hormonal contraceptives (oral contraceptive, patch, vaginal ring, injectables, or implants), intrauterine devices, vasectomy, or barrier methods of contraception in conjunction with spermicide. Hormonal contraceptives must be on a stable dose for at least 4 weeks before baseline (Day 0).

   Note: Women of nonchildbearing potential are as follows:
   - Women who have had surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation)
   - Women ≥60 years of age
   - Women >40 and <60 years of age who have had a cessation of menses for at least 12 months and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (FSH ≥40 mIU/mL) or cessation of menses for at least 24 months without FSH levels confirmed
10. Women of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test at baseline (Day 0).
11. Subject must have negative tuberculosis (TB) infection tests. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test, T-spot test or a Quantiferon Gold test, and with a chest x-ray, if one has not been performed in the last 6 months. Subject who demonstrates evidence of latent TB infection (either PPD greater than or equal to 5 mm of induration or positive Quantiferon Gold or T-spot test, irrespective of Bacillus Calmette–Guérin (BCG) vaccination status and negative chest x-ray findings for active TB, or suspicious chest x-ray findings) will not be allowed to participate in the study.

Confidential and proprietary. Permission should be obtained before any reproduction.

12. Subject must be willing to participate and must be capable of giving informed consent, and the consent must be obtained prior to any study-related procedures.

Exclusion Criteria:

Subjects will not be eligible for participation in the study if they meet any of the following criteria at the screening and baseline (Day 0) visits, unless specified otherwise:

1. Female subject who is breastfeeding, pregnant, or who is planning a pregnancy during the study.
2. Subject has evidence of erythrodermic, pustular, predominantly guttate psoriasis, or drug-induced psoriasis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Subject is known to have immune deficiency or is immunocompromised.
5. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to baseline (Day 0). Subjects with successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
6. Subject has had a major surgery within 8 weeks prior to baseline (Day 0) or has a surgery planned during the study.
7. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
8. Subject has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values $\geq$ 2 times the upper limit of normal (ULN) at screening.
9. Subject has absolute neutrophil count $\leq$1,5 X 10^9/L or platelet count $\leq$100 X 10^9/L at screening.
10. Subject has history of clinically significant anemia or hemoglobin (Hgb) value $\leq$ 10 g/dL at screening.
11. Subject has a creatinine clearance $\leq$ 60 ml/min at screening (calculated with Cockcroft-Gault formula)
12. Subject with positive results for hepatitis B surface antigens (HBsAg), anti-hepatitis B core antibodies (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
13. Subject has a known or suspected allergy to CUDC-305 or any component of the investigational product.
14. Subject has a history of clinically significant drug or alcohol abuse in the last year prior to baseline visit (Day 0).

Confidential and proprietary. Permission should be obtained before any reproduction.

15. Subject is currently receiving an investigational product or device or has received one within 4 weeks prior to baseline visit (Day 0).
16. Subject has used biologics medication 12 weeks prior to baseline visit (Day 0), or 5 half-lives (whichever is longer).
17. Subject has used any systemic treatment for psoriasis (including corticosteroids, oral retinoids, immunosuppressive medication, methotrexate, cyclosporine, or apremilast) within 4 weeks prior to baseline visit (Day 0).
18. Subject has used any topical medication to treat psoriasis (including corticosteroids; retinoids; vitamin D analogues, such as calcipotriol; or tar) within 2 weeks prior to baseline visit (Day 0).
19. Subject had any UVB phototherapy (including tanning beds) or excimer laser within 2 weeks prior to baseline visit (Day 0).
20. Subject had PUVA treatment within 4 weeks prior to baseline visit (Day 0).
21. Subject has received a live attenuated vaccine within 4 weeks prior to baseline visit (Day 0) or plan to receive a live attenuated vaccine during the study and up to 1 month after the last study drug administration.Subject had excessive sun exposure within 2 weeks prior to baseline visit (Day 0), or is planning a trip to a sunny climate, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended for other circumstances when exposure cannot be avoided. Sunscreen must not be applied on the clinic visit days before the visit.
22. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
23. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
24. Subject is taking anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets (nonsteroidal anti-inflammatory drugs [NSAIDs] and low-dose aspirin that is equal or lower than 81 mg will not be considered antiplatelets), or has a contraindication to skin biopsies.

Statistical Analysis:

Because of the nature and design of the study, the statistical analysis will be mainly descriptive.

Descriptive summaries of demographics, baseline characteristics, and subject disposition will be presented by dose regimen and overall. Continuous variables will be summarized by dose regimen and overall in tables and will include the number of subjects, mean, standard deviation, median, minimum, maximum, and range. Categorical variables will be presented by dose regimen and overall in tables as frequencies and percentages.

No formal sample size calculations were conducted. Four subjects will be enrolled into each cohort, for a total of a maximum of 16 subjects. This sample size was selected to allow sufficient characterization of the drug's safety profile over the planned doses range and to allow for

Confidential and proprietary. Permission should be obtained before any reproduction.

preliminary efficacy assessment of CUDC-305 in subjects with moderate to severe plaque psoriasis.

Confidential and proprietary. Permission should be obtained before any reproduction.

1 BACKGROUND

Psoriasis is a chronic inflammatory skin disease characterized by immune dysregulation of unknown etiology affecting over 25 million individuals worldwide (1, 2). Psoriasis can become debilitating and severely impact quality of life, well-being and personal interactions (3, 4). An estimated 25% of patients suffer moderate to severe disease forms that require systemic therapy with immune suppressants and ultraviolet phototherapy (5, 6). Despite advances in the development of targeted biologics including TNF, IL-12/23 and IL-17 inhibitors, most psoriasis patients remain inadequately treated and dissatisfied with the therapy they are receiving (7, 8). Due to the risk of serious adverse side effects associated with these therapies, patients are often required to alternate between various therapeutic modalities as a precautionary measure. There is a pressing need for the clinical development of effective, safe, easy to use, and affordable psoriasis therapeutics that target the upstream proteomic mediators of the disease.

Human psoriatic lesions display a profound upregulation of HSP90 as compared to normal skin which is thought to be partially associated with IL-17 production (9, 10). CUDC-305 (previously called Debio 0932) is a novel small molecule HSP90 inhibitor which displays promising pharmacological properties for drug development in psoriasis such as good oral bioavailability, potent HSP90 inhibition, accumulation in the skin (as demonstrated in preclinical models), no ocular toxicity, a good safety profile (demonstrated in a Phase 1 oncology dose escalation study), a pharmacokinetic profile (high first-past metabolism) that permits rapid flexibility in terms of dose-control/ therapy discontinuation, and targeting of multiple upstream mediators of inflammatory pathways. Clinical investigation in psoriasis is supported by evaluation of anti-psoriatic potential in human epidermal keratinocyte and monocytic cell lines showing that HSP90 inhibition with CUDC-305 is highly effective in inhibiting proliferation in keratinocytes and monocytes, and reducing the secretion of inflammatory cytokines in activated monocytes and T-cells.

In clinically relevant animal models of psoriasis, oral delivery of CUDC-305 resulted in clinically significant alleviation of psoriasis, reduced epidermal thickness, and dramatic reduction in levels of TNFα and IL-17, pro-inflammatory cytokines linked to the persistence of psoriasis (11). Clinical safety of CUDC-305 has been validated in a CUDC-305 Phase 1 trial for oncology indication. Interestingly during that study, a patient with severe psoriasis covering more than 40% of the skin surface showed complete remission after 43 days of treatment with 800 mg CUDC-305 daily (11). These serendipitous clinical findings in association with supporting preclinical data in three different murine clinical investigations support the clinical investigation of the safety and efficacy of CUDC-305 in the treatment of moderate to severe plaque psoriasis.

The clinic lack of activity on pharmacodynamic markers, the lack of clear relationship between dose/exposure or toxicity/signs of activity, a high intra- and inter patient variability, lower than expected plasma levels based on pharmacological models and a poor oral availability despite a good absorption due to extensive metabolism were referenced in the **Declaration of the End of Trial Form** as reasons for the discontinuation of the trial: *A Phase I-II evaluation of the safety and efficacy of the oral HSP90 inhibitor Debio-0932 in combination with standard of care in first- and*

Confidential and proprietary. Permission should be obtained before any reproduction.

second-line therapy of patients with Stage IIIb or IV Non-small Cell Lung Cancer - the HALO study (HSP90 inhibition And Lung cancer Outcomes), during Part A. It is important to highlight that this study was completed in patients with advanced cancers, specifically Stage IIIb and IV Non-small Cell Lung Cancer (NSCLC), where CUDC-305 administration was being evaluated in combination with cisplatin/pemetrexed and cisplatin/gemcitabine (naive Stage IIIb and IV NSCLC patients) or with docetaxel (previously treated Stage IIIb and IV NSCLC). The proposed trial is designed as a dose-ranging trial in order to explore dose and define the maximum tolerated dose and viable Phase 2 doses in patients with moderate to severe psoriasis (the target population); a unique population that is quite disparate from that of previous trials. Furthermore, discontinuation of the referenced Phase 2 studies were not based on safety concerns and that all safety observations from these studies "were consistent with the previously observed side effects." Finally, preclinical studies found that CUDC-305 accumulated in dermal tissues versus plasma(11). In a xenograft mouse model of psoriasis daily dosing of CUDC-305 lead to plasma levels of ~2uM and skin levels of ~24 pmol/mg of wet tissue 30 minutes post-dosing on the final treatment day, representing a concentration in skin that exceeds the IC50 (~0.1 μM) of CUDC-305 for HSP90α/β (based on the assumption that 1mg of tissue equals 1 ml of biological fluid and taking in to account the 6% unbound plasma fraction of CUDC-305). This suggests that concerns with reduced efficacy being associated with poor oral bioavailability may be less relevant in dermal indications, such as psoriasis.

Confidential and proprietary. Permission should be obtained before any reproduction.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is as follows:

- To determine the optimal efficacious dose-range of CUDC-305 in the treatment of moderate to severe plaque psoriasis in a Phase 1b proof-of-concept study

2.2 Secondary Objectives

The secondary objectives are as follows:

- To evaluate the safety and tolerability of CUDC-305 in the treatment of moderate to severe plaque psoriasis
- To investigate changes in skin and blood biomarkers

Confidential and proprietary. Permission should be obtained before any reproduction.

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary efficacy endpoint is as follows:

- Change from baseline in Psoriasis Area and Severity Index (PASI) score at Week 12

3.2 Secondary Endpoints

The secondary endpoints are as follows:

Efficacy Endpoints

- Proportion of subjects with Physician's Global Assessment (PGA) of clear or almost clear at Weeks 2, 4, 8, 12, and 16
- Change and percent change from baseline in body surface area (BSA) covered with plaque psoriasis at Weeks 2, 4, 8, 12, and 16
- Change and percent change from baseline in BSA multiplied by the PGA at Weeks 2, 4, 8, 12, and 16
- Proportion of subjects achieving 50%, 75%, and 90% reduction from baseline in PASI at Weeks 2, 4, 8, 12, and 16
- Change and percent change from baseline in PASI scores at Weeks 2, 4, 8, and 16
- Percent change from baseline in PASI scores at Week 12
- Change from baseline in pruritus Numeric Rating Scale (NRS) at Weeks 2, 4, 8, 12, and 16
- Change from baseline in the Dermatology Life Quality Index (DLQI) total score at Weeks 4, 8, 12, and 16
- Change from baseline in skin and blood biomarkers at Weeks 4, 8, and 12

Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of related TEAEs

Confidential and proprietary. Permission should be obtained before any reproduction.

4 STUDY DESIGN

This is a 12-week treatment, singlecenter, open-label, single-arm, dose-selection, proof-of-concept study to determine a dosage of CUDC-305 that is tolerable and demonstrates preliminary efficacy for use in future efficacy Phase 2 trials.

Eligible subjects will be sequentially assigned to one of the four cohorts (approximately n = 4 per cohort) receiving ascending or descending doses of CUDC-305. The first cohort will be administered a starting oral dose of 250 mg/d for 12 weeks, which is believed to be the target effective dose for treatment of psoriasis. The dose regimen to be administered to the subsequent cohort will be decided after reviewing the safety and efficacy data of the first four subjects completing the treatment period (12 weeks) in the current cohort. A safety meeting will take place to review the available data prior to deciding the next dose and then initiating dosing of the subsequent cohort. The doses that will be evaluated in this study range between 100 mg and 1000 mg and may include: 100 mg, 250 mg, 500 mg, 800 mg, or 1000 mg orally once daily.

The sponsor and principal investigator(s) will jointly evaluate the safety and tolerability of CUDC-305 at the safety meeting, and intolerability will be determined by taking into account all information from adverse events (AEs), vital signs, physical examination findings, laboratory abnormalities, and electrocardiogram (ECG) findings. The study may be stopped permanently or interrupted at any time for safety reasons.

PASI, PGA, BSA, pruritus NRS, and DLQI will be performed to assess efficacy. Safety will be assessed with the vital signs, physical examination, clinical laboratory tests, ECG, and collection of AEs.

Skin biopsies will be collected from nonlesional and lesional skin for immunohistochemistry and gene expression analysis.

Medical photographs of the target lesion will also be performed at each study visit (except the screening visit).

A schedule of events is presented in Section 7.

Confidential and proprietary. Permission should be obtained before any reproduction.

5 STUDY POPULATION

This study will include approximately 16 subjects with moderate to severe plaque psoriasis. Subjects will be men or women, aged 18 years or older.

Subjects who are discontinued after taking the first dose of study product will not be replaced.

5.1 Inclusion Criteria

Subjects will be eligible to be enrolled in the study if they meet all of the following criteria at the screening and baseline (Day 0) visits, unless specified otherwise:

1. Men or women aged 18 years or older at the time of consent.
2. Subject has a history of plaque psoriasis for at least 6 months prior to the screening visit.
3. Subject has stable psoriasis conditions for at least 3 months before screening, according to subject.
4. Subject has plaque psoriasis covering ≥3% of his total BSA at baseline (Day 0).
5. Subject has a PASI score of ≥6 at baseline (Day 0).
6. Subject has a PGA score of ≥3 at baseline (Day 0).
7. Subject has a body mass index (BMI) ≤40 kg/m^2.
8. Subject is a candidate for phototherapy or systemic treatement of psoriasis (either naïve or has a history of previous treatment).
9. Subjects (women and men) involved in any sexual intercourse that could lead to pregnancy must agree to use an effective contraceptive method from at least 4 weeks before baseline (Day 0) until at least 4 weeks after the last study product administration for the duration of the study. Effective contraceptive methods are: systemic hormonal contraceptives (oral contraceptive, patch, vaginal ring, injectables, or implants), intrauterine devices, vasectomy, or barrier methods of contraception in conjunction with spermicide. Hormonal contraceptives must be on a stable dose for at least 4 weeks before baseline (Day 0).

   Note: Women of nonchildbearing potential are as follows:
   - Women who have had surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation)
   - Women ≥60 years of age
   - Women >40 and <60 years of age who have had a cessation of menses for at least 12 months and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (FSH ≥40 mIU/mL) or cessation of menses for at least 24 months without FSH levels confirmed
10. Women of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test at baseline (Day 0).

Confidential and proprietary. Permission should be obtained before any reproduction.

11. Subject must have negative tuberculosis (TB) infection tests. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test, T-spot test or a Quantiferon Gold test, and with a chest x-ray, if one has not been performed in the last 6 months. Subject who demonstrates evidence of latent TB infection (either PPD greater than or equal to 5 mm of induration or positive Quantiferon Gold or T-spot test, irrespective of Bacillus Calmette–Guérin (BCG) vaccination status and negative chest x-ray findings for active TB, or suspicious chest x-ray findings) will not be allowed to participate in the study.
12. Subject must be willing to participate and must be capable of giving informed consent, and the consent must be obtained prior to any study-related procedures.

5.2 Exclusion Criteria

Subjects will not be eligible for participation in the study if they meet any of the following criteria at the screening and baseline (Day 0) visits, unless specified otherwise:

1. Female subject who is breastfeeding, pregnant, or who is planning a pregnancy during the study.
2. Subject has evidence of erythrodermic, pustular, predominantly guttate psoriasis, or drug-induced psoriasis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Subject is known to have immune deficiency or is immunocompromised.
5. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to baseline (Day 0). Subjects with successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
6. Subject has had a major surgery within 8 weeks prior to baseline (Day 0) or has a surgery planned during the study.
7. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
8. Subject has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥ 2 times the upper limit of normal (ULN) at screening.
9. Subject has absolute neutrophil count $\leq 1{,}5 \times 10^9$/L or platelet count $\leq 100 \times 10^9$/L at screening.
10. Subject has history of clinically significant anemia or hemoglobin (Hgb) value ≤ 10 g/dL at screening.
11. Subject has a creatinine clearance ≤ 60 ml/min at screening (calculated with Cockcroft-Gault formula)

Confidential and proprietary. Permission should be obtained before any reproduction.

12. Subject with positive results for hepatitis B surface antigens (HBsAg), anti-hepatitis B core antibodies (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
13. Subject has a known or suspected allergy to CUDC-305 or any component of the investigational product.
14. Subject has a history of clinically significant drug or alcohol abuse in the last year prior to baseline visit (Day 0).
15. Subject is currently receiving an investigational product or device or has received one within 4 weeks prior to baseline visit (Day 0).
16. Subject has used biologics medication 12 weeks prior to baseline visit (Day 0), or 5 half-lives (whichever is longer).
17. Subject has used any systemic treatment for psoriasis (including corticosteroids, oral retinoids, immunosuppressive medication, methotrexate, cyclosporine, or apremilast) within 4 weeks prior to baseline visit (Day 0).
18. Subject has used any topical medication to treat psoriasis (including corticosteroids; retinoids; vitamin D analogues, such as calcipotriol; or tar) within 2 weeks prior to baseline visit (Day 0).
19. Subject had any UVB phototherapy (including tanning beds) or excimer laser within 2 weeks prior to baseline visit (Day 0).
20. Subject had PUVA treatment within 4 weeks prior to baseline visit (Day 0).
21. Subject has received a live attenuated vaccine within 4 weeks prior to baseline visit (Day 0) or plan to receive a live attenuated vaccine during the study and up to 1 month after the last study drug administration.Subject had excessive sun exposure within 2 weeks prior to baseline visit (Day 0), or is planning a trip to a sunny climate, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended for other circumstances when exposure cannot be avoided. Sunscreen must not be applied on the clinic visit days before the visit.
22. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
23. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
24. Subject is taking anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets (nonsteroidal anti-inflammatory drugs [NSAIDs] and low-dose aspirin that is equal or lower than 81 mg will not be considered antiplatelets), or has a contraindication to skin biopsies.

5.3 Discontinuations

Subjects have the right to withdraw from the study at any time for any reason without penalty. The investigator also has the right to withdraw subjects from the study if he or she feels it is in the best interest of the subject or if the subject is uncooperative or noncompliant.

Confidential and proprietary. Permission should be obtained before any reproduction.

Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the follow-up examination.

The investigator or one of his or her staff members should contact the subject to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded. The criteria for enrollment must be followed explicitly. Subjects who discontinue the study after taking his or her first dose will be asked, if they agree, to come for a last assessment (early termination visit). Subjects who discontinue will not be replaced.

Reasons for discontinuation include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made because of a serious adverse event (SAE), the study product is to be discontinued immediately and appropriate measures are to be taken. The investigator will notify the sponsor immediately.
- The attending physician requests that the subject be withdrawn from the study.
- The subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented.
- The sponsor or regulatory authorities, for any reason, stop the study. In this case, all subjects will be discontinued from the study and notified of the reasons for the discontinuation.
- The subject has become pregnant at any time during the study.
- Other: the subject may withdraw from the study for any other reason, including withdrawal of consent.

Confidential and proprietary. Permission should be obtained before any reproduction.

6 TREATMENT

6.1 Treatment Administration

Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study. Each subject should read and sign an informed consent form prior to any screening procedures being performed. This study involves the investigational study product CUDC-305 (also known as Debio 0932) administered orally once daily early in the morning for 12 weeks at approximately the same time (± 1 hour) every day. Various doses, starting at 250 mg and ranging between 100 mg to 1000 mg, will be administered in each cohort to determine the dose to be used in future efficacy Phase 2 trials in psoriasis.

6.2 Study Treatment

6.2.1 Description

CUDC-305 is formulated as a round red coated tablet for daily oral administration containing various amounts of the active compound.

6.2.2 Storage Conditions

The study product will be provided by Regranion to the investigator. It will be kept on site in a secure, temperature-controlled place between 15°C and 30°C and will only be supplied to subjects in the trial under the supervision of the investigator. Room temperature on site will be monitored and recorded.

6.2.3 Study Product Dispensing and Return

The study product will be dispensed by the study site during the treatment period to the subject at each study visit (except at the Week 1 visit). Subjects are to return all study product (used and unused) to the study site at the Week 1, 2, 4, 6, 8, 10, and 12 visits. The number of capsules will be counted prior to dispensing and upon return, and the counts will be recorded in the source documents and case report form (CRF). Each subject is to be instructed on the importance of returning study product at the next study visit. If a subject does not return study product, he or she will be instructed to return it as soon as possible.

6.2.4 Study Product Accountability

The investigator is responsible for maintaining accurate records of the study product received initially and of the study product dispensed/used. After verification of the product accountability by the sponsor or designee, used product will be stored safely until destruction/return. Any study product accidentally or deliberately destroyed, or returned to the sponsor or designee will be accounted for. Any discrepancies between amounts dispensed and returned will be explained.

Confidential and proprietary. Permission should be obtained before any reproduction.

All study product accountability forms and treatment logs must be retained in the investigator's study file. Product inventory and accountability records will be maintained as per Good Clinical Practice (GCP) and International Council for Harmonisation (ICH) guidelines. These records must be available for inspection at any time by the sponsor, its designees, or by regulatory agencies.

6.2.5 Rationale for Selection and Timing of Doses in the Study

The goal of this trial is to explore dose and define the recommended dose for future Phase 2 studies in psoriasis. Based on previously completed Phase 1 safety and pharmacokinetic analyses, the maximum tolerated dose (MTD) of CUDC-305 was determined to be 1,000 mg/d, thus defining the upper limit of this Phase 1b trial. The starting dose for this study will be 250 mg/d which corresponds to 1/4 of the MTD of the previous Phase 1 clinical study and is based on the NOAEL of the 28-day toxicity studies and cardiovascular assessment study in dogs. The doses that will be evaluated in this study range between 100 mg and 1000 mg and may include: 100 mg, 250 mg, 500 mg, 800 mg, or 1000 mg orally once daily.

6.2.6 Method of Assignment to Treatment Dose

Eligible subjects will be sequentially assigned to one of the four cohorts (approximately n = 4 per cohort) receiving ascending or descending doses of CUDC-305. The first cohort will be administered a starting oral dose of 250 mg/d which is believed to be the target effective dose for treatment of psoriasis. The dose regimen to be administered to the subsequent cohort will be decided after reviewing the safety and efficacy data of the first four subjects completing the treatment period (12 weeks) in the previous cohort. The dose regimen of the subsequent cohort could be higher or lower, according the safety and efficacy data of the previous cohort. A safety meeting will take place to review the available data prior to deciding the next dose and then initiating dosing of the subsequent cohort. The study may be stopped permanently or interrupted at any time for safety reasons following review of study data.

6.2.7 Safety Monitoring Rules

If a severe AE or SAE is reported in any dose cohort, the study may be suspended pending review of the safety data or unless the investigator determines that the event is unrelated to the study product.

The sponsor, in consultation with the investigator(s), may decide to stop or modify the dose escalation at any time for safety reasons following review of study data.

6.2.8 Breaking of Study Blinding

This is an open-label study, therefore no unblinding procedure is planned for this study.

6.2.9 Assessment of Treatment Adherence

Subject adherence to treatment with CUDC-305 will be assessed at each visit. Adherence to treatment will be assessed by direct questioning, review of the subject's dosing diary, and by

Confidential and proprietary. Permission should be obtained before any reproduction.

maintaining adequate product dispensing records. Any deviation from the prescribed dosage regimen will be recorded in the source document and CRF.

If there is a discrepancy between the subject dosing diary entries and the capsule count, assessment of treatment adherence will be based on the latter.

Subjects who are significantly non-adherent to treatment will be counseled and could be discontinued from the study, at the discretion of the Investigator.

6.3 Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, and antacids) taken within 4 weeks prior to screening and throughout the study must be recorded.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries will include the dose, unit, frequency of administration, route of administration, start date, discontinuation date, and indication. If the medication is discontinued or the dosage is changed, these details must be recorded.

6.3.1 Permitted Therapies

6.3.1.1 Emollients

Subjects can apply a bland emollient of their choice, except emollients containing salicylic acid, on their skin including on psoriasis lesions during the entire duration of the study. Emollient must not be applied on the clinic visit days before the visit.

Every effort should be made to keep the same emollient throughout the study. The complete commercial name of the selected emollient(s) will be recorded in the source document and the CRF. No other products may be applied to the lesions during the study.

6.3.2 Prohibited Therapies or Procedures

The following therapies are prohibited:

- Use of biologics medication 12 weeks prior to baseline visit (Day 0), or 5 half-lives (whichever is longer) and throughout the study
- Use of any systemic treatment for psoriasis (including corticosteroids, oral retinoids, immunosuppressive medication, methotrexate, cyclosporine, or apremilast) within 4 weeks prior to baseline visit (Day 0) and throughout the study
- Use of any topical medication or topical medical devices to treat psoriasis (including corticosteroids; retinoids; vitamin D analogues, such as calcipotriol; or tar) within 2 weeks prior to baseline visit (Day 0) and throughout the study
- Use of anticoagulant medication (e.g., heparin, LMW-heparin, warfarin, antiplatelets [NSAIDs and low-dose aspirin that is equal or lower than 81 mg will not be considered antiplatelets])

Confidential and proprietary. Permission should be obtained before any reproduction.

- Use of UVB phototherapy (including tanning beds) or excimer laser within 2 weeks prior to baseline visit (Day 0)
- Use of PUVA treatment within 4 weeks prior to baseline visit (Day 0)
- Excessive sun exposure within 2 weeks prior to baseline visit (Day 0), or planning a trip to a sunny climate, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided. Sunscreen must not be applied on the clinic visit days before the visit.

Confidential and proprietary. Permission should be obtained before any reproduction.

7 SCHEDULE OF EVENTS

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the informed consent form. No treatment or trial-related procedures will be initiated before the informed consent is signed. The baseline (Day 0) visit must be performed, at the latest, 30 days after the screening visit.

The screening evaluation will be performed according to the inclusion and exclusion criteria. If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Table 1 provides a description of the procedures to be performed at each visit.

Confidential and proprietary. Permission should be obtained before any reproduction.

Table 1: Schedule of Events

	Screening	Baseline /Day 0							End of Treatment/ ET	Follow-up
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Week	**–4**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Day ±Window (days)	**–30 to –1 Days**	**0**	**7 ±1 Day**	**14 ±1 Day**	**28 ±2 Days**	**42 ±2 Days**	**56 ±2 Days**	**70 ±2 Days**	**84 ±2 Days**	**112 ±4 Days**
Informed consent	X									
Demographics	X									
Medical and surgical history, including smoking status and psoriatic arthritis evaluation[1]	X	X								
Inclusion/exclusion criteria	X	X								
Pregnancy test[2]	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X			X		X		X	X[3]
ECG	X								X	X[3]
Weight, height and BMI[4]	X	X							X	
Vital signs	X	X	X	X	X	X	X	X	X	X
Chemistry and hematology laboratory panel	X	X			X		X		X	X[3]
Serology (HBV, HCV, HIV)	X									
Chest x-ray[5]	X									
PPD, T-spot test or Quantiferon Gold[5]	X									
PASI	X	X	X	X	X	X	X	X	X	X
PGA	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X
Pruritus NRS	X	X	X	X	X	X	X	X	X	X
DLQI questionnaire		X			X		X		X	X
Psoriatic arthritis evaluation					X		X		X	X
Identification of target lesion		X								

Confidential and proprietary. Permission should be obtained before any reproduction.

	Screening	Baseline /Day 0							End of Treatment/ ET	Follow-up
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Week	**–4**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Day ±Window (days)	**–30 to –1 Days**	**0**	**7 ±1 Day**	**14 ±1 Day**	**28 ±2 Days**	**42 ±2 Days**	**56 ±2 Days**	**70 ±2 Days**	**84 ±2 Days**	**112 ±4 Days**
Medical photographs of target lesion		X	X	X	X	X	X	X	X	X
Collection of skin biopsies[6]		X			X		X		X	
Study product administration on site		X								
Study product dispensing		X		X	X	X	X	X		
Collect study product/study product accountability			X	X	X	X	X	X	X	
Subject dosing dairy distribution/collection/review		X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Adverse events evaluation		X	X	X	X	X	X	X	X	X

BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ET = early termination (visit); HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; PBMC = peripheral blood mononuclear cell; PGA = Physician's Global Assessment; PPD = purified protein derivative.

Note:

[1] Smoking status: never smoked, past smoker, active smoker. For past smoker and active smoker, record the number of years, number of cigarettes per day, and when applicable year stopped.

[2] Women of childbearing potential only; serum pregnancy test at the screening visit and urine pregnancy test at the other visits.

[3] Only if clinically significant changes are detected at Week 12.

[4] Height will be measured at screening visit only, and BMI will be calculated at screening and baseline (Day 0) visits.

[5] If one has not been performed in the last 6 months.

[6] Skin biopsies on nonlesional skin at baseline and on the target lesion at baseline, Week 4, Week 8, and Week 12 for gene expression and immunohistochemistry staining.

Confidential and proprietary. Permission should be obtained before any reproduction.

8 STUDY ASSESSMENTS

8.1 Efficacy Assessments

Clinical evaluations of psoriasis will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given subject whenever possible.

8.1.1 Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) is a scale from 0 to 72 that is regularly used in plaque psoriasis studies (12, 13). Refer to APPENDIX A for a complete description of this scale. The PASI will be evaluated at the visits specified in Section 7. To be eligible for this study, subjects must have a PASI of ≥ 6 at baseline (Day 0).

8.1.2 Physician's Global Assessment

The Physician's Global Assessment (PGA) of disease severity will be assessed at the visits specified in Section 7. The PGA is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity; assessment will be determined according to the following categories: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe)(14). To be eligible for this study, subjects must have a PGA score of ≥ 3 at the baseline (Day 0) visit. The PGA should be performed at arm's length distance from the subject. A detailed description of PGA scores is provided in Table 2.

Table 2: Physician's Global Assessment of Disease Severity in Psoriasis

Score	Grade	Description
0	Clear	No signs of psoriasis, postinflammatory hyperpigmentation may be present
1	Almost clear	No thickening, normal to pink coloration, no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bight to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

8.1.3 Body Surface Area

The overall BSA affected by psoriasis will be evaluated (from 0% to 100%) at the visits specified in Section 7. One subject's palm represents 1% of his/her total BSA. To be eligible, subjects must have a BSA of ≥ 3% at baseline (Day 0).

Confidential and proprietary. Permission should be obtained before any reproduction.

8.1.4 Pruritus Numeric Rating Scale

The intensity of pruritus will be recorded at the visits specified in Section 7 using a Pruritus Numeric Rating Scale (15). This will be evaluated by asking subjects to assign a numerical score representing the current intensity of their symptoms over the last 24h on a scale from 0 to 10, with 0 for having no symptoms and 10 having worst imaginable symptoms. The NRS of pruritus is provided in APPENDIX B.

8.2 Quality-of-Life Assessments

8.2.1 Dermatology Life Quality Index Questionnaire

The Dermatology Life Quality Index (DLQI) is a simple 10-question validated questionnaire that has been used in more than 40 different skin conditions. Its use has been described in more than 1,000 publications, including many multinational studies. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. It will be completed at the visits specified in Section 7. The questionnaire is provided in APPENDIX C.

8.3 Safety Assessments

8.3.1 Vital Signs

The following vital signs will be recorded at every visit with the subject in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), and body temperature (°C).

Weight (kg) and height (cm) will be collected to calculate the Body Mass Index (BMI) which will be recorded at the screening and baseline (Day 0) visits. The height will only be recorded once at the screening visit and the same value will be used for BMI calculation at baseline (Day 0). The weight will be recorded at screening, baseline (Day 0), and at the Week 12 visit (end of treatment visit).

If deemed appropriate by the investigator, clinically significant findings in the vital signs will exclude a subject from study participation. Any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE if this abnormality was not present at the baseline (Day 0) visit or is assessed as having worsened since baseline (Day 0). Any change in health between the informed consent form and the first study drug administration will be recorded as medical history.

8.3.2 Physical Examination

The following sites/systems will be included in the physical examination to be performed at the visits specified in Section 7. In case clinically significant findings are detected at Week 12, the physical examination may be repeated at Week 16. Each system will be scored as normal/abnormal

Confidential and proprietary. Permission should be obtained before any reproduction.

(nonclinically significant or clinically significant). Pertinent details must be recorded for any clinically significant findings.

- General appearance
- Dermatological (except psoriasis)
- Head, eyes, ears, nose, throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from study participation. Any significant change will be reported as an AE if this abnormality was not present at the baseline (Day 0) visit or is assessed as having worsened since baseline (Day 0). Any change in health between the informed consent form and the first study drug administration will be recorded as medical history.

8.3.3 Clinical Laboratory Tests

Laboratory tests will be performed at the visits specified in Section 7. In case clinically significant findings are detected at Week 12, the corresponding laboratory test may be repeated at Week 16. The tests will include hematology with differential and a standard chemistry panel (chemistry includes liver function tests). A serum pregnancy test will be performed at screening, and a urine pregnancy test will be performed at all the other study visits for women of childbearing potential. In addition, serology testing (HBV, HCV, HIV) and tuberculosis test (PPD, T-spot test or Quantiferon Gold, if one has not been performed in the last 6 months) will be performed at the screening visit only.

All routine laboratory tests will be analyzed at the local laboratory of each trial site.

The specific tests in these panels are listed in Table 3:

Confidential and proprietary. Permission should be obtained before any reproduction.

Table 3: Clinical Laboratory Testing

Laboratory Testing	Tests Included
Hematology	HCT, Hgb, MCH, MCHC, MCV, MPV, platelets, RBC, WBC and differentials (neutrophils, lymphocytes, monocytes, eosinophils and basophils relative and absolute).
Serum chemistry	Albumin, alkaline phosphatase, ALT, AST, chloride, CK, creatinine (enzymatic), GGT, glucose random, HbA1c, LDH, potassium, sodium, total bilirubin, urea (BUN), uric acid, cholesterol, triglycerides
Pregnancy test	β-hCG in serum for females of childbearing potential at screening only and urine pregnancy test at the other visits.
Laboratory tests required at screening only	FSH levels for women greater than 40 and less than 60 years of age who have had a cessation of menses for at least 12 months but less than 24 months. Tuberculosis test (PPD, T-spot test or Quantiferon Gold), and serology (HBV [HBsAg, anti-HBc], HCV, HIV)

ALT = alanine aminotransferase; anti-HBc = anti–hepatitis B core antibodies; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; BUN = blood urea nitrogen; CK = creatine kinase; FSH = follicle-stimulating hormone; GGT = gamma-glutamyltransferase; HBsAg = hepatitis B surface antigens; HBV = hepatitis B virus; HCT = hematocrit; HCV = hepatitis C virus; Hgb = hemoglobin; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC= mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MPV = mean platelet volume; PPD = purified protein derivative; RBC = red blood cell (count); WBC = white blood cell (count).

If deemed appropriate by the investigator and in accordance with the exclusion criteria described in Section 5.2, clinically significant findings in clinical laboratory testing will exclude a subject from study participation. Any significant change will be reported as an AE if this abnormality was not present at the baseline (Day 0) visit or is assessed as having worsened since baseline (Day 0). Any change in health between the informed consent form and the first study drug administration will be recorded as medical history.

8.3.4 Electrocardiogram

Twelve-lead ECGs will be performed as a safety assessment at the visits specified in Section 7. In case clinically significant findings are detected at Week 12, the ECG may be repeated at Week 16. Clinically significant findings in the ECG will exclude a subject from study participation (as deemed appropriate by the investigator). Any significant change will be reported as an AE if this abnormality was not present at baseline (Day 0) visit or is assessed as having worsened since baseline (Day 0).

8.3.5 Chest X-Ray

In addition to PPD, T-spot test or Quantiferon Gold, a chest x-ray will be performed at screening only (if one has not been performed in the last 6 months) to assess the presence of tuberculosis.

Confidential and proprietary. Permission should be obtained before any reproduction.

8.4 Other Assessments

Refer to the study manual for detailed instructions on tube labeling, sample collection, processing, storage, shipping, and laboratories in charge of the analyses below.

8.4.1 Skin Biopsies

All subjects will have two 4.0-mm skin biopsy taken from a nonlesional area at the baseline (Day 0) visit and two 4.0-mm biopsy taken from the target lesion at baseline (Day 0), Week 4, Week 8, and Week 12 visits, for a total of 10 biopsies.

The first half will be used for immunohistochemistry staining and will be proceed in OCT.

The second half will be processed in RNAlater and used for gene expression analysis using reverse transcription polymerase chain reaction (RT-PCR).

The skin will be cleaned, disinfected, and anesthetized before skin biopsies are performed. Sterile gauze will be used to absorb any bleeding. The biopsy sites will be cauterized and sutured if necessary.

8.4.2 Medical Photography

Medical photographs of another lesion than the target lesions will be performed at baseline (Day 0) and at all subsequent visits (if no other lesions are present on the body, photographs could be performed on a biopsied lesion). Care will be taken to use the same camera, the same magnification, and the same settings for each photograph at each visit in order to obtain comparable pictures. Medical photography will be taken using a blue background.

Photographs will be identified as follows: study number, subject number, subject initials, visit name, and date. Photographs will be kept as electronic files on site and will be transmitted to the sponsor for review.

8.4.3 Status of Psoriatic Arthritis

Subjects suffering from psoriatic arthritis (as reported in the subject's medical history at screening) will be asked at the visits specified in Section 7 if their condition has improved, remained stable, or worsened) since the screening visit.

Confidential and proprietary. Permission should be obtained before any reproduction.

9 ADVERSE EVENTS

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, without regard to the possibility of a causal relationship with this treatment.

Investigators are responsible for monitoring the safety of subjects who are participating in this study and for alerting the sponsor of any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for appropriate medical care of subjects during the study.

The investigator remains responsible for following through with an appropriate health care option for all AEs that are serious or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or stable. Follow-up frequency is left to the discretion of the investigator.

Safety will be evaluated by collecting information on AEs and by accessing data from vital signs, ECGs, physical examinations, and laboratory results.

Prior to subject enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s) in the appropriate section of the source document and CRF. During the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any AEs.

If a subject exp eriences an AE at any time after the first dose of the study product, the event will be recorded as an AE in the source document and CRF.

9.1 Adverse Event Causality

The investigator will establish causality of the AE to the experimental treatment. The investigator should take into account the subject's history, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine causality of an AE:

- Not related: Temporal relationship of the onset of the AE, relative to the experimental treatment, is not reasonable, or another cause can explain the occurrence of the AE.
- Related: Temporal relationship of the onset of the AE, relative to the experimental treatment, is reasonable, follows a known response pattern to the treatment, and an alternative cause is unlikely.

Confidential and proprietary. Permission should be obtained before any reproduction.

9.2 Adverse Event Severity

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: The symptom is barely noticeable to the subject and does not influence performance of daily activities. Treatment is not ordinarily indicated.
- Moderate: The symptom is sufficiently severe to make the subject uncomfortable, and performance of daily activities is influenced. Treatment may be necessary.
- Severe: The symptom causes severe discomfort, and daily activities are significantly impaired or prevented. Treatment may be necessary.

9.3 Serious Adverse Events

If a subject experiences an SAE at any time after the first study product administration, the event will be recorded as an SAE in the source document and CRF.

A serious adverse event or reaction is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

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; or development of drug dependency or drug abuse.

Confidential and proprietary. Permission should be obtained before any reproduction.

9.3.1 SAE Reporting

All SAEs, related to the experimental treatment or not, occurring during the course of the study must be reported on an SAE form to the sponsor within 24 hours of the knowledge of the occurrence. (This refers to any AE that meets one or more of the aforementioned serious criteria.) The SAE reporting period ends at the Follow-up visit (Week 16).

Reporting should be done by sending the completed SAE Report Form to the following e-mail address (faxing can also be done as a second option in case e-mailing is not possible).

Contact name: Dr. Anne Bregnhøj
Department of Dermatology, Aarhus University Hospital
P.P. Orumsgade 11, DK-8000 Aarhus C
Denmark
E-mail: annebreg@rm.dk
Phone: +45 21835720
Fax: +45 78461824

The sponsor will evaluate all SAEs as soon as the reports are received and will assess the expectedness of each SAE in relation to the study treatment. For each SAE received, the sponsor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met. The sponsor or designee will manage the expedited reporting of relevant safety information to concerned regulatory agencies in accordance with local laws and regulations.

9.4 Pregnancy Reporting

If a female subject or a female partner of a male subject becomes pregnant during the study, the subject should inform the study site as soon as possible. Upon confirmation of the pregnancy, the female subject will be discontinued from the study. The investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy and send it to the sponsor within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). Posttreatment follow-up should be done to ensure subject safety. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, to 1 month of age in that infant. The investigator will notify the sponsor of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the sponsor and ethics committee.

9.5 Suspected Unexpected Serious Adverse Reactions

If a subject experience a SUSAR at any time after the first study product administration, the event will be recorded as a SUSAR in the source document and CRF.

Confidential and proprietary. Permission should be obtained before any reproduction.

SUSARs meets the same criteria as SARs, but are not expected to occur according to the reference safety informations in the Investigator´s Brochure.

9.5.1 SUSAR Reporting

All SUSARs occurring during the course of the study must be reported on a SUSAR form to the sponsor within 24 hours of the knowledge of the occurrence.

Reporting should be done by sending the completed SUSAR Report Form to the following e-mail address (faxing can also be done as a second option in case e-mailing is not possible).

Contact name: Dr. Anne Bregnhøj
Department of Dermatology, Aarhus University Hospital
P.P. Orumsgade 11, DK-8000 Aarhus C
Denmark
E-mail: annebreg@rm.dk
Phone: +45 21835720
Fax: +45 78461824

Sponsor must ensure that all relevant information about SUSARs, which is fatal or life threatening, is recorded and reported to Danish Medicines Agency and the Ethical Committee no later that 7 days after sponsor has been informed about such a serious reaction. No later than 8 days after initial reporting sponsor must inform the Danish Medicines Agency and the Ethical Committee about follow-up information and action taken.

Any other SUSARs must be reported to Danish Medicines Agency and the Ethical Committee no later that 15 days after sponsor has been informed about them.

SUSAR´s from non-EU/EEA countries shall not be reported to the Danish Medicines Agency.

Confidential and proprietary. Permission should be obtained before any reproduction.

10 SAMPLE SIZE AND STATISTICAL METHODS

10.1 Determination of Sample Size

No formal sample size calculations were conducted. Six subjects will be enrolled into each cohort, for a total of maximum 16 subjects. This sample size was selected to allow sufficient characterization of the drug's safety profile over the planned doses range and to allow for preliminary efficacy assessments of CUDC-305 in subjects with moderate to severe plaque psoriasis.

10.2 Statistical and Analytical Plans

Because of the nature and design of the study, the statistical analysis will be mainly descriptive.

Descriptive summaries of demographics, baseline characteristics, and subject disposition will be presented by dose regimen and overall. Continuous variables will be summarized by dose regimen and overall in tables and will include the number of subjects, mean, standard deviation, median, minimum, maximum, and range. Categorical variables will be presented by dose regimen and overall in tables as frequencies and percentages.

Even if not sample size calculation was performed we bring a power analysis for the primary endpoint: PASI at week 12. A non parametric Wilcoxon signed-rank test will allow us to determine that Change in PASI is significant different form 0 with 80% power and 95% confidence level if the observed effect size is greater or equal to 1.23 standard deviation.

10.2.1 Subject Disposition

Efficacy will be evaluated on the basis of the intent-to-treat (ITT) population. A supportive analysis will also be conducted on the per-protocol (PP) population.

The intent-to-treat (ITT) population will include all subjects who received at least one dose of the study product.

The per-protocol (PP) population will include all subjects who received at least one dose of the study product with no significant protocol deviations.

The safety population (SAF) will be defined as all subjects who received at least one dose of the study product.

10.2.2 Efficacy Analysis

The primary and secondary efficacy analyses will be summarized and presented descriptively. No statistical comparison per se will be performed. However, comparison between the different doses tested may be performed.

Confidential and proprietary. Permission should be obtained before any reproduction.

10.2.3 Safety Analysis

Safety analysis will be summarized and presented descriptively by evaluating the incidence of TEAEs and drug-related TEAEs.

10.2.4 Interim Analysis

No formal interim analysis of the study endpoints is planned for this study. However, reviews of available safety data and preliminary efficacy data to guide decisions regarding the subsequent cohorts (dose decision) will be conducted by the sponsor and/or investigator(s) on an ongoing basis. Because this is an open-label study, the unblinding is not to be taken into consideration for the safety meetings.

Beyond the mainly descriptive analysis by using regular measures of central tendency and measures of dispersion, the continuous endpoints as Changes and Percentages of Changes can be assessed and tested with a mixed- effect model (Fixed-factors: treatment and time, random intercept for each patient). The least square mean and standard error of the mean will be exposed on proper plots and tables. Proportion of subjects at each time point for efficacy and safety endpoints can be compared by using contingency tables and Fisher exact test.

Confidential and proprietary. Permission should be obtained before any reproduction.

11 DATA QUALITY ASSURANCE/SITE MONITORING

During the study, monitoring visits will be performed at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the CRFs, product accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

The site may be audited or monitored or both by a quality assurance officer named by the sponsor, and regulatory authorities may wish to perform on-site audits. The investigator will be given notice before an audit occurs and will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

12 DATA COLLECTION AND RETENTION

The investigator must maintain source documents for each subject in the study. These source documents will consist of case and visit notes (clinical medical records) containing demographic and medical information and the results of any tests or assessments. Subject data will be transcribed by site personnel into a paper CRF. All information on the CRFs must be traceable to these source documents in the subject's file. The data collected will be entered in a database system thereafter. Data listings will be reviewed, and manual queries will be generated and sent to the site if necessary.

13 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that the subjects' anonymity will be maintained and that subjects' identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrolment log relating codes with the names of subjects. The investigator should maintain in strict confidence documents not for submission to the sponsor (e.g., subjects' written consent forms).

14 INVESTIGATOR'S FILES AND RETENTION OF DOCUMENTS

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories: Investigator Study File and subject clinical source documents.

The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Confidential and proprietary. Permission should be obtained before any reproduction.

15 ETHICS

15.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2008) and that are consistent with Good Clinical Practice ICH Tripartite Guideline (July 2002) and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

15.2 Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by a research ethics board/institutional review board (REB/IRB). This board must operate in accordance with the current federal regulations. For sites with a local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor (or contract research organization) prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

15.3 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study. It must also be explained to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

If new safety information results in significant changes in the risk/benefit assessment, or if any new information becomes available that may affect the willingness of a subject to continue to participate, the consent form should, if necessary, be reviewed and updated by the REB/IRB. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form, and asked to give their consent to continue in the study.

15.4 Risk: Benefit

Psoriasis is a serious chronic disease associated with significant morbidity and impairment. The disease is usually not life threatening and does not induce irreversible injury to skin or other organs, with the exception of psoriatic arthritis. Psoriasis is however, considered to be a systemic inflammatory disease, and patients with psoriasis have an increased risk of comorbidities related to the metabolic syndrome, including adiposity, arterial hypertension and abnormalities in lipid and glucose metabolism (Reich K, JEADV 2012). This leads to an increased risk of cardiovascular complications among patients with psoriasis compared to controls. A recent study has shown that treatment with potent anti-inflammatory drug (biologics) in patients with severe psoriasis was associated with reduced coronary artery disease progression monitored by CT scans compared with a control group (Hjuler KF, JAMA Dermatol 2016).
Currently used immunosuppressants and antimetabolites are associated with potentially serious side effects include life-threatening infections and neoplasms. Reports indicate that although dermatologists are aware of the national treatment guidelines for psoriasis(16), less than 50% of

Confidential and proprietary. Permission should be obtained before any reproduction.

patients with moderate-to-severe psoriasis receive systemic treatment(17). This deficiency has been linked to elevated safety concerns(17). Indeed, due to the risk of serious adverse side effects associated with these therapies patients are often required to alternate between various therapeutic modalities as a precautionary measure. Recent publications indicate that oral therapeutics, particularly those without immunosuppressive side-effects, remain a critical unmet need for patients that are unwilling or unable to use injectable treatments(18). Thus, while current guidelines recommend systemic treatment with immunomodulatory biologics(5), in order to achieve adequate disease control in patients with moderate-to-severe psoriasis, efficacious oral psoriasis therapeutics with a strong safety profile that also have a pharmacokinetic profile that permits the management of spontaneously arising adverse effects. The goal of therapy is to bring disease under control by using the least toxic therapy, where drugs associated with risk of serious irreversible toxicity or mortality should be reserved for patients with severe, recalcitrant psoriasis. Potentially serious although reversible gastrointestinal toxicities could be associated with CUDC-305. Although not evident in human studies, preclinical animal data also suggest a potential for an increased QTc intervals in the heart following CUDC-305 and treated patients will be required to undergo mandatory cardiac monitoring. *In vitro* studies suggest that high doses of CUDC-305 may have off-target effects on opioid receptors. Quality of life and study product accountability will be closely monitored. To further mitigate risk during study enrollment all available safety and efficacy data will be reviewed by the principal investigator (PI) or delegate and the sponsor's medical monitor before subsequent cohorts are dosed. A safety meeting will take place to review the available data prior to deciding the next dose and then initiating dosing of the subsequent cohort. The study may be stopped permanently or interrupted at any time for safety reasons following review of study data. If any subject from the sentinel cohort experiences a severe or clinically significant adverse event (AE) that is considered possibly drug-related, then dosing of the remaining cohorts with higher doses will not be conducted. Dose escalation can only proceed if all parties (PI or delegate and the sponsor's medical monitor) agree that it is safe to do so and will be documented in the form of a signed dose decision document. Participants will be closely monitored at all times during the study by experienced medical, nursing and clinical staff. In the event of an unexpected AE or medical emergency the participant will be transferred to a hospital for further management this will be implemented without delay. Phase I clinical studies support a favorable toxicity profile of CUDC-305 and the overall risk:benefit, considering all aspects detailed above, is considered to be acceptable to support commencing the study in patients with moderate to severe psoriasis.

16 PUBLICATION POLICY

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol. The trial will be registered on ClinicalTrials.Gov prior to the first subject being dosed.

Confidential and proprietary. Permission should be obtained before any reproduction.

17 REFERENCES

1. Lowes MA, Suarez-Farinas M, Krueger JG. Immunology of psoriasis. Annual review of immunology. 2014;32:227-55.
2. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. Journal of the American Academy of Dermatology. 2014;70(3):512-6.
3. Pfohler C, Muller CS, Vogt T. Psoriasis vulgaris and psoriasis pustulosa - epidemiology, quality of life, comorbidities and treatment. Current rheumatology reviews. 2013;9(1):2-7.
4. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. The journal of investigative dermatology Symposium proceedings / the Society for Investigative Dermatology, Inc [and] European Society for Dermatological Research. 2004;9(2):136-9.
5. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. Journal of the European Academy of Dermatology and Venereology : JEADV. 2009;23 Suppl 2:1-70.
6. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. Journal of the American Academy of Dermatology. 2008;58(5):826-50.
7. Horn EJ, Fox KM, Patel V, Chiou CF, Dann F, Lebwohl M. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. Journal of the American Academy of Dermatology. 2007;57(6):957-62.
8. Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. JAMA dermatology. 2013;149(10):1180-5.
9. Kumar P, Kolls JK. Act1-hsp90 heats up TH17 inflammation. Nature immunology. 2013;14(1):16-7.
10. Kakeda M, Arock M, Schlapbach C, Yawalkar N. Increased expression of heat shock protein 90 in keratinocytes and mast cells in patients with psoriasis. Journal of the American Academy of Dermatology. 2014;70(4):683-90 e1.
11. Stenderup K, Rosada C, Gavillet B, Vuagniaux G, Dam TN. Debio 0932, a new oral Hsp90 inhibitor, alleviates psoriasis in a xenograft transplantation model. Acta dermato-venereologica. 2014;94(6):672-6.
12. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.
13. Marks R, Barton SP, Shuttleworth D, Finlay AY. Assessment of disease progress in psoriasis. Archives of dermatology. 1989;125(2):235-40.
14. Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat. 2015;26(1):23-31.
15. Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. Acta dermato-venereologica. 2012;92(5):502-7.
16. Nast A, Mrowietz U, Kragballe K, Puig L, Reich K, Warren RB, et al. National and multinational guidelines in Europe: results from an online survey on awareness of different

Confidential and proprietary. Permission should be obtained before any reproduction.

national and European psoriasis guidelines. Archives of dermatological research. 2013;305(7):637-43.
17. Nast A, Mrowietz U, Kragballe K, de Jong EM, Puig L, Reich K, et al. Barriers to the prescription of systemic therapies for moderate-to-severe psoriasis--a multinational cross-sectional study. Archives of dermatological research. 2013;305(10):899-907.
18. Mahmood T, Zaghi D, Menter A. Emerging oral drugs for psoriasis. Expert opinion on emerging drugs. 2015;20(2):209-20.

Confidential and proprietary. Permission should be obtained before any reproduction.

APPENDIX A: Psoriasis Area and Severity Index

PASI Scoring

Four anatomic sites – head, upper extremities, trunk and lower extremities – are assessed for erythema, induration (infiltration, plaque thickness), and desquamation (scaling) as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The area affected by psoriasis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = < 10%
- 2 = 10 to < 30%
- 3 = 30 to < 50%
- 4 = 50 to < 70%
- 5 = 70 to < 90%
- 6 = 90 to 100%

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs anteriorly

The PASI score for each body region is obtained by using the formula

$$PASI = 0.1\ (E_h + I_h + D_h)\ A_h + 0.2\ (E_u + I_u + D_u)\ A_u + 0.3\ (E_t + I_t + D_t)\ A_t + 0.4\ (E_l + I_l + D_l)\ A_l$$

Where *E*, *I*, *D*, and *A* denote erythema, induration, desquamation, and area, respectively, and *h*, *u*, *t,* and *l* denote head, upper extremities, trunk, and lower extremities, respectively.

Confidential and proprietary. Permission should be obtained before any reproduction.

APPENDIX B: Numeric Rating Scale

Numeric Rating Scale (NRS)
0 1 2 3 4 5 6 7 8 9 10 No itch Worst imaginable itch

Confidential and proprietary. Permission should be obtained before any reproduction.

APPENDIX C: Dermatology Life Quality Index

Subject ID #: ___ ___ - ___ ___ ___ Subject Initials: ___ ___ ___

Visit Day: _____ Visit Date (dd-mmm-yyyy):_____

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	□ □ □ □	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	□ □ □ □	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	□ □ □ □	Not relevant □
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	□ □	Not relevant □
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	□ □ □	

Confidential and proprietary. Permission should be obtained before any reproduction.

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □

©AY Finlay, GK Khan, April 1992 www.dermatology.org.uk.

Please check you have answered EVERY question. Thank you.

Confidential and proprietary. Permission should be obtained before any reproduction.