A multicenter, open label, single-arm pilot study to evaluate the efficacy and safety of oral apremilast in patients with moderate to severe palmoplantar pustulosis (PPP) (APLANTUS)

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Study Phase:	Phase II
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1 Study Synopsis

Study Title	A multicenter, open label, single-arm pilot study to evaluate the efficacy and safety of oral apremilast in patients with moderate to severe palmoplantar pustulosis (PPP) (APLANTUS)
Short Title	APLANTUS
Protocol No.	069-008
Internal Study Code	AP-CL-PSOR-PI-006639
EudraCT No.	2016-005122-11
Clinical Phase	Phase II
Study Design	Multicenter, open label, single-arm pilot study
Study Objective(s)	The primary objective of this study is: • To demonstrate a significant improvement of Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) at week 20 compared with baseline in moderate to severe chronic palmoplantar pustulosis under apremilast therapy. The secondary objectives of the study are: • To evaluate an improvement of PPPASI at all assessment times compared with baseline in moderate to severe chronic palmoplantar pustulosis under apremilast therapy. • To evaluate differences during the treatment with apremilast in life quality assessment measures: Dermatology Life Quality Index (DLQI) at all assessment times compared with baseline • To evaluate safety of apremilast in patients with moderate to severe palmoplantar pustulosis Exploratory objectives are: • Time course of Hand and Feet Physician Global Assessment (H&F PGA) at all assessment times. • Pustules count 50 response and Pustules count 75 response, defined as a 50% and 75% decrease in Pustules count from baseline, during the 20 weeks treatment period • To evaluate differences in the mean change from baseline at all assessment times of Visual Analogue Scale (VAS) discomfort / pain, VAS pruritus / itch at all assessment times relatively to day 0 (baseline) • To evaluate changes in Psoriasis Area Severity Index (PASI), Physician Global Assessment (PGA) and dynamic PGA if plaque psoriasis is present between baseline and all assessment times • To explore the effect of apremilast on serum / plasma immunological markers • To explore the effect of apremilast on immunological markers in skin biopsy samples (sub-study)
Approximate Duration of Study	The study is estimated to have duration of approximately 11 months from first patient in (FPI) to last patient out (LPO). Enrolment will cease if the target number of patients is reached.

Duration of Patient Participation	Up to 4 weeks screening period, 20 weeks treatment period
Number of Visits	5
Approx. Number of Sites	5 in Germany
Number of Patients	20
Target Disease	Palmoplantar pustulosis (PPP)
Criteria for Inclusion	• Male and female patients aged 18 years or more at screening visit. • Patients with chronic PPP (disease history of at least 6 months of diagnosis), who are eligible for treatment with systemic therapy defined as having PPP inadequately controlled by topical treatment and / or phototherapy and / or previous systemic therapy • Patients with chronic moderate to severe PPP defined as patients with a PPPASI ≥ 12 with or without concomitant plaque-type psoriasis • Negative result of a urine pregnancy test taken at screening and at baseline for all women, except those who are surgically sterile or at least 1 year postmenopausal (i.e. at least 12 consecutive months with amenorrhea without other known or suspected medical cause) • Willingness and capability of using a highly effective contraceptive measure from Screening visit until the end of at least one menstrual cycle (but not less than 28 days) following discontinuation of apremilast as defined below: o Female patient of childbearing potential (fertile, following menarche and until becoming post-menopausal unless permanently sterile) using a highly effective method of contraception OR female patients of non-childbearing potential (surgically sterilized [e.g. hysterectomy, bilateral salpingectomy and bilateral oophorectomy] or post-menopausal) o Male patient, and his female partner of childbearing potential, using a highly effective method of contraception o Adequate contraceptive method defined as: ▪ A method with less than 1% failure rate (e.g. permanent sterilization, hormone implants, hormone injections, some intrauterine devices, or vasectomized partner) OR ▪ The use of two methods of contraception (e.g. one barrier method [condom, diaphragm or cervical/vault caps] with spermicide and one hormonal contraceptive [e.g. combined oral contraceptives, patch, vaginal ring, injectables and implants]) • Patient is capable of understanding and giving written, voluntary informed consent before study screening. • Willingness and capability of complying with all study procedure requirements, as per the Investigator's judgment

	(e.g. patient able to swallow the apremilast tablets, blood sampling).
Criteria for Exclusion	General • Pregnant or breast-feeding women • Current or history of psychiatric disease that would interfere with the ability to comply with the study protocol or give informed consent • Patients known to have had a substance abuse (drug or alcohol) problem within the previous 12 months • Individuals who are involved in the organization of the study • Patients who are in any way dependent on the investigator • Patients who are participating in a clinical study • Relatives, partner or staff of any clinical site personnel Disease-related • Evidence of skin conditions (e.g. eczema) other than PPP / psoriasis that would interfere with evaluations of the effect of study medication on PPP or psoriasis. • Laboratory values available from routine blood test taken within 8 weeks prior to screening with any of the following: o Serum creatinine >1.4 x upper limit of normal (ULN) for age and gender o Estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m^2 according to the CKD-EPI equation • Pustular psoriasis lesions on the part of body other than hands or feet • Significant concurrent medical conditions at the time of screening, including: o Risk factors for renal toxicity (renal inflammation) o Severe hepatic dysfunction o Unstable angina pectoris o Uncompensated congestive heart failure o Severe pulmonary disease requiring hospitalization or supplemental oxygen therapy o Immunodeficiency disorders: primary or secondary o Known positive HIV test result, hepatitis B surface (HBS) antigen or hepatitis C (HCV) test result o Uncontrolled Insulin-dependent diabetes mellitus o Cancer or history of cancer (except for resected cutaneous basal cell or squamous cell carcinoma) in the last 5 years o Open cutaneous ulcers • Any condition that, in the judgment of the investigator, might cause this study to be detrimental to the patient. Medication-related • Ultraviolet B (UVB) therapy, topical steroids, topical calcineurin inhibitors, topical Vitamin A or D analog preparations, or anthralin within 14 days of baseline • Exceptions: low potency topical corticosteroids (class I and II, according to European classification for potency of topical corticosteroids) will be allowed as therapy for the face, groin, axillae in accordance with the manufacturer's suggested usage dose

	• Psoralen plus ultraviolet A radiation (PUVA), ciclosporin, acitretin, alitretinoin, alefacept (Amevive®), anakinra (Kineret®), systemic corticosteroids, methotrexate, fumaric acids or any other systemic anti-psoriasis therapy within 28 days of baseline • Prior (within the last 2 years) or concomitant use of antipsoriatic biologic therapy with Tumor Necrosis Factor (TNF)-α blocker and / or ustekinumab and / or ixekizumab and / or secukinumab and / or brodalumab and / or guselkumab • Concomitant use of strong cytochrome P450 3A4 (CYP3A4) enzyme inductors (e.g. rifampicin, phenobarbital, carbamazepin, phenytoin and St. John`s wort) • Use of an investigational drug within 4 weeks prior to baseline or 5 pharmacokinetic / pharmacodynamics half-lives (whichever is longer) • Prior treatment with apremilast / Otezla® • Receipt of any live (attenuated) vaccine within 28 days prior to baseline. • Concomitant use of any other phosphodiesterase 4 inhibitor • Patients with hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption • For patients with skin biopsy samples taken: patients with clinically relevant coagulation disorders or medication or known hypersensitivity against local anesthetics
Investigational Medicinal Product (Including Placebo and Active Comparator, If Any)	Apremilast (Otezla®)
Dosage and Administration	Apremilast BID, orally Day 1: 10 mg in morning Day 2: 10 mg in morning and 10 mg in evening Day 3: 10 mg in morning and 20 mg in evening Day 4: 20 mg in morning and 20 mg in evening Day 5: 20 mg in morning and 30 mg in evening Day 6 and thereafter: 30 mg twice daily
Concomitant Treatment	Required concomitant medication (except those listed under exclusion criteria) for the treatment of concomitant diseases and not known to interfere with the study drug or to mask the effect of the study drug, is unrestricted and may be continued during the study. Low potency topical corticosteroids (class I and II, according to European classification for potency of topical corticosteroids) will be allowed as background therapy for the treatment of the face, axillae, and groin in accordance with the manufacturer's suggested usage during the course of the study except for lesions selected for clinical evaluations. An unmedicated skin moisturizer (without urea) is permitted for body lesions only. Patients should not use the unmedicated skin moisturizer within 12 hours prior to the clinic visit on lesions selected for clinical evaluations.

Efficacy Evaluation	Efficacy will be assessed by evaluating PASI, PPPASI, PGA, dynamic PGA, H&F PGA, pustules count, VAS for pruritus / itch and discomfort / pain on hands and feet, DLQI, and immunological markers.
Safety and Tolerability Evaluation	Safety will be assessed by evaluating Adverse Events (AEs), vital signs and physical examination.
Primary Endpoint	Percentage change from baseline in PPPASI after 20 weeks of treatment with apremilast
Secondary Endpoints	• Absolute and percent change from baseline in PPPASI during the 20 weeks treatment period • PPPASI 50 response and PPPASI 75 response, defined as a 50% and 75% decrease in PPPASI from baseline, during the 20 weeks treatment period • DLQI bands (0-1 no effect, 2-5 small effect, 6-10 moderate effect, 11-20 very large effect, 21-30 extremely large effect on the disease related quality of life) during the 20 weeks treatment period • Absolute and percent change from baseline in DLQI during the 20 weeks treatment period • Safety as assessed by AEs, vital signs and physical examination
Exploratory Endpoints	• Absolute and percentage change from baseline in level of immunological markers in plasma / serum during the 20 weeks treatment period with apremilast • Percentage change from baseline in level of immunological markers in skin biopsy samples after 20 weeks of treatment with apremilast (sub-study)
Data Analysis / Statistical Methods	This is a pilot study intended to gain first information on the possible clinical and mechanistical effects of apremilast on PPP; therefore the sample size is not based on statistical considerations. The Full Analysis Set (FAS) is defined as all patients who received at least one dose of study drug and the Per Protocol Set (PP) is defined as all patients who received at least one dose of study drug who completed the study with no major protocol violations. These two analysis sets will be used for analyses of efficacy endpoints. The definition of the PP set will be finalized in the data review meeting prior to database closure. In general, categorical variables will be summarized using frequencies and percentages and continuous variables will be summarized using number of observations, mean, standard deviation, median, minimum, first quartile, third quartile, and maximum. The primary endpoint percent change from baseline in PPPASI after 20 weeks of treatment will be summarized as continuous variable together with 95%-confidence limits. Statistical comparison between post- versus pre-treatment values will be done based on the Wilcoxon signed-rank test with two-sided p-value <0.05 indicating significance. Missing values will be replaced

	using last-observation-carried-forward (LOCF) method for the analysis of the primary endpoint based on the FAS. Exploratory endpoints (plasma / serum immunological marker analysis and the skin biopsy immunological marker (sub-study)) will be analyzed outside of the study setting by a research laboratory (Psoriasis Research and Treatment Center, University Hospital Charité, Berlin, Germany). Statistical comparison between post- versus pre-treatment values will be done based on the Wilcoxon signed-rank test with two-sided p-value <0.05 indicating significance.
Ethical Considerations	This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the ICH E6 guideline and the ethics principles that have their origins in the Declaration of Helsinki. The independent ethics committee and the competent authority must review and approve the study before any patients are enrolled. Consent must be obtained from the patient using the approved informed consent form (ICF) before any procedures specified in the protocol are performed. The data acquisition meets all requirements of data protection for each individual patient, since all patient-related documentation can only be identified by a patient identification number. All personal information of the patient is accessible only to the treating physician.

Study Flow Chart

Phase	**Screening**	**Treatment Phase**				
Visits	V1	V2 Baseline	V3	V4	V5 End of Study	Early Termi-nation
Week	-4 - -1	0	4	12	20	
Day	-28 - -1	0	28 ± 4	84 ± 4	140 ± 7	
In- / exclusion criteria	x	x	-	-	-	-
Pregnancy test[1]	x	x	x	x	x	x
Informed consent	x	-	-	-	-	-
Demography, educational status	x	-	-	-	-	-
Medical and psoriasis history, prior medication	x	-	-	-	-	-
PsA, comorbidity	x	x	-	x	x	x
Concomitant medications	x	x	x	x	x	x
Nicotine anamnesis	x	-	-	-	x	-
Physical examination incl. weight and height[2] (BMI)	x	x	-	-	x	x
Vital signs[3]	x	x	x	x	x	x
Results of routine blood test / urinalysis available[4]	x	-	-	-	-	-
Investigator assessments						
PASI	-	x	x	x	x	x
PPPASI	x[5]	x	x	x	x	x
PGA	-	x	x	x	x	x
H&F PGA	-	x	x	x	x	x
Dynamic H&F PGA	-		x	x	x	x
Pustules count	-	x	x	x	x	x
Patient reported outcomes						
VAS (pruritus / itch and discomfort / pain) on hands and feet	-	x	x	x	x	x
DLQI	-	x	-	x	x	-
Photographs[6] (optional)	-	x	-	-	x	-
Serum and plasma	-	x	x	x	x	x
Biopsies[7] (optional sub-study)	-	x	-	-	x	x
Documentation for drug accountability and treatment compliance	-	x	x	x	x	x
Medication dispensing[8]	-	x	x	x	-	-
Return of study medication	-	-	x	x	x	x
AEs / SAEs	x	x	x	x	x	x
Reason for discontinuation						x

1. Urine pregnancy test for female patients of childbearing potential
2. Only at V1: height
3. Sitting blood pressure and pulse rate
4. Within the ranges given in the exclusion criteria **not older than 8 weeks** prior to screening
5. For inclusion PPPASI must be ≥ 12
6. From both hands and feet (optional)
7. Two lesional biopsies from feet or hands (optional)
8. Including instructions for medication intake

AE / SAE	Adverse Event / Serious Adverse Event
BMI	Body Mass Index
DLQI	Dermatology Life Quality Index
H&F PGA	Hand and Feet Physician Global Assessment
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PPPASI	Palmoplantar Pustulosis Psoriasis Area and Severity Index
PsA	Psoriasis Arthritis
V	Visit
VAS	Visual Analogue Scale

2 Table of Contents

2.1 List of Tables

3 Contacts

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Laboratory(ies) or medical / technical departments	
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4 Signature Page

The signatures below document the approval of this protocol, and provide the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to all applicable laws and regulations including, but not limited to, the Medicinal Products Act (Arzneimittelgesetz AMG) (1), the international Good Clinical Practice guideline (GCP) (ICH E6) (2) and the ethics principles that have their origins in the Declaration of Helsinki (3).

Prof. Dr. Kristian Reich
Sponsor

07 - JUN - 2018
Date

Dr. Wilsmann-Theis
Coordinating Investigator

07 Jun 2018
Date

Dr. Thomas Bickert
TFS Trial Form Support GmbH
Project Leader

07 - Jun - 2018
Date

Johanna Bewert
TFS Trial Form Support GmbH
Statistician

07 - Jun - 2018
Date

Dr. Wiebke Griemberg
TFS Trial Form Support GmbH
Author of the protocol

07 - JUN - 2018
Date

Statement(s) of Principal Investigator(s)

I have thoroughly read this study protocol and have understood the requirements as well as the conditions of this clinical study protocol. I agree to following points:

- to perform the clinical study according to this protocol and all applicable laws and regulations including, but not limited to, the Medicinal Products Act (Arzneimittelgesetz AMG) (1), the international Good Clinical Practice guideline (ICH E6) (2)and the ethics principles that have their origins in the Declaration of Helsinki (3)
- to record accurately all required data on the case report forms (CRFs)
- to provide direct access to source data / documents (source document verification)
- to permit study-related monitoring, audits, IRB / IEC review, and regulatory inspections
- to use the study material only as specified in this protocol
- to report within 24 hours any adverse event that is serious, whether considered treatment-related or not
- to instruct and train all delegates in my institution, who will take over tasks within this clinical study

Principal Investigator:

_____

Name

_____ _____

Signature Date

5 List of Abbreviations and Definition of Terms

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT (sGPT)	Alanine transaminase (serum glutamic-pyruvic transaminase)
AMG	Medicinal Products Act (Arzneimittelgesetz)
AST (sGOT)	Aspartate transaminase (serum glutamic-oxaloacetic transaminase)
ATC-Code	Anatomic-Therapeutically-Chemical Code
BGB	Bürgerliches Gesetzbuch (civil code of Germany)
BID	Bis in die (twice a day)
BMI	Body Mass Index
cAMP	Cyclic adenosine monophosphate
CCL2	Chemokine (C-C motif) ligand 2
CCR2	C-C chemokine receptor type 2
CD11c+	Integrin alpha X chain protein-positive
CKD-EPI	Chronic Kidney Diseas-Epidemiology Collaboration
CPMP / CHMP	Committee for Proprietary Medicinal Products, now CHMP, Committee for Medicinal Products for Human Use
CRF	Case Report Form
CRO	Contract Research Organization
CXCL8	CXC-Motiv-Chemokin 8 (= IL8)
CYP3A4	Cytochrome P450 3A4
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme Linked Immunosorbent Assay
FAS	Full Analysis Set
FPI	First Patient In
GCP	Good Clinical Practice
H&F PGA	Hand and Feet Physician Global Assessment
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form

ICH	International Council for Harmonization (formerly the International Conference on Harmonization)
ID	Identification
IEC	Independent Ethics Committee
IFN-γ	Interferon- γ
IL	Interleukin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
LPO	Last Patient Out
MACE	Major Adverse Cardiac Events
MBO	(Model) Professional Code for Physicians in Germany
MCP-1	Monocyte chemoattractant protein-1 (= CCL2)
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
n, N	Number
PASI	Psoriasis Area and Severity Index
PDE / PDE4	Phosphodiesterase / Phosphodiesterase 4
PGA	Physician Global Assessment
PP	Per Protocol (set)
PPP	Palmoplantar pustulosis
PPPASI	Palmoplantar Pustulosis Psoriasis Area and Severity Index
PPPASI 50 / 75	50% / 75% decrease in PPPASI
PsA	Psoriasis Arthritis
PT	Preferred Term
PUVA	Psoralen plus ultraviolet A radiation
qPCR	Real-time Polymerase Chain Reaction on reverse transcribed mRNA
RMP	Risk Management plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
sP-selectin	Soluble P-selectin
ThX	T Helper Cell X

TNF	Tumor Necrosis Factor
TEAE	Treatment emergent AE
ULN	Upper limit of normal
UVB	Ultraviolet B
V	Visit
VAS	Visual Analogue Scale
WHO	World Health Organization

Definitions

Baseline	Data collected for all patients at the beginning of a clinical study before any study treatment. These data include demographics, such as age and gender, and study-specific measures.
Eligible Patient	Any potential participant who upon entrance into the treatment phases of the study meets all of the inclusion criteria and none of the exclusion criteria set forth in the protocol and had signed a valid Ethics Committee (EC) approved informed consent form.
End of Study / Study Completion Date	Final date on which data is collected (i.e. date of the last visit of the last patient).
Screening	Evaluation of patients for participation in a clinical study according to inclusion and exclusion criteria.

6 Introduction

Psoriasis in difficult to treat locations includes visible and therefore stigmatizing body regions such as the hands, the face and the scalp. Other difficult to treat areas may impact the daily life aspects and function such as palms and soles and / or nails. Under normal conditions, these locations require particular management and have a significant impact on the health-related quality of life (physical, functional, emotional impact) (4-6). As this is such an important factor for the patients it is often higher ranking than corresponding disease indexes.

6.1 Background and Rationale

Palmoplantar pustulosis (PPP) is a rare condition in which erythematous and scaly plaques studded with sterile pustules persist on the palms or soles. The disease is chronic and very resistant to treatment. It is much more common in those who smoke (or have smoked in the past). PPP is a disease of adults and is rare in children. It usually starts in the fifth or sixth decade of life, although age of onset can also be earlier.

In most series, there has been a predominance of women. The disease presents itself with one or more well-delineated scaly erythematous plaques. Within this plaque, pustules are present, usually 2-5mm in diameter. Fresh pustules are yellow; older ones are yellow-brown or dark brown as the pustule dries up. Eventually, the desiccated pustule is exfoliated. Usually, pustules in all stages of evolution are seen. Itching is variable, but often serious; often, the patients report a 'burning' discomfort in the lesions. On the hands, the thenar eminence is the predilection site. On the feet, the instep, the medial or lateral border of the foot at the level of the instep, or the sides or back of the heel are frequently involved. A striking symmetry of the lesions on the hands or feet is common, but sometimes a solitary lesion may persist for weeks or months before other lesions appear. Additionally, patients are often unable to walk or to work due to the pain and thus are severely affected in activities of daily life (7).

Palmoplantar pustulosis is a therapeutically challenging condition that can significantly impact patient quality of life (8). It often affects smokers, but quitting smoking does not always help clear the disease. Apart from intense topical therapy (with or without occlusion), phototherapy, and psoralen plus ultraviolet A (PUVA), oral retinoids (acitretin) have traditionally been the first drug of choice. Phototherapy including PUVA therapy has the disadvantage, apart from cancerogenicity, that it has to be performed several times per week at an outpatient clinic or a private practice of a dermatologist. Acitretin is usually not given to girls and women of childbearing potential due to its teratogenic potential that persists for up to three years after discontinuation of the drug. Methotrexate or cyclosporine have been described to be effective in PPP in some patients as well (9-12). Alternative treatment options for patients with PPP who do not respond to conventional antipsoriatic therapies include the use of antimycotics (13) or antibiotics (14), which have been described in single case reports and studies. However, oral alitretinoin treatment has recently been proven not to be effective (15).

Several biologics that have been approved for plaque-type psoriasis have been tried in small case series or small studies in the treatment of PPP.

Ustekinumab, a monoclonal antibody targeting Interleukin (IL)-12/23 has been tried in the treatment of PPP, but results have been ambiguous. In a case series of four patients, two failed to improve (16). Bissonnette et al. (17) were not able to show clinical benefit with licensed doses of ustekinumab, while others recently presented a series of five, respectively nine, case reports successfully treated with ustekinumab (18;19).

A small placebo-controlled pilot study (n=15) with etanercept, a fusion protein targeting Tumor Necrosis Factor (TNF)-α, at a dose of 50 mg twice weekly, showed a statistically significant difference in Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) response

at 24 weeks. At 12 weeks etanercept was numerically, but not statistically significantly better than placebo (20).

Alefacept is approved for plaque-type psoriasis in the United States but not in Europe and has been reported to be moderately effective in PPP with reductions in PPPASI of 49,6% after 16 weeks of treatment (21).

Despite the impact of PPP on daily activities including the ability to work, few clinical studies address treatment, and there is a lack of data and quality-of-life assessment during therapy beyond anecdotal case reports and small studies as described above (9;10;13;14;16-18;20;21).

Only Acitretin, Dapsone and glucocorticosteroids have the approval for the treatment of pustular skin diseases, and no other systemic antipsoriatic treatment has been approved for PPP.

Biologics are approved for plaque-type psoriasis and/or psoriasis arthritis, and they have also been described in some investigations to be successful in patients with PPP (17;18;20;21). However, there are no published phase III trials of biologics in the indication PPP, and treatment of PPP with biologics or traditional antipsoriatic drugs, with the exception of acitretin, can only be performed in an off-label setting.

Moreover, treatment of PPP often does not achieve a lasting good clinical response or may have to be discontinued due to side effects.

Apremilast (Otezla®, marketing authorization holder Celgene Europe Ltd., approved for treatment of Psoriasis and Psoriasis Arthritis in Europe), an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro- and anti-inflammatory mediators. PDE 4 is a cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase (PDE) and the dominant PDE in inflammatory cells. Inhibition of PDE4 elevates intracellular cAMP levels, which in turn downregulates the inflammatory response by modulating the expression of TNF-α, IL-23, and other inflammatory cytokines. Elevation of cAMP also increases anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriasis and psoriatic arthritis. Interestingly, apremilast has anti-inflammatory effects on a wide variety of cell types. Not only does it exert anti-inflammatory effects on T-cells, but also on immune cells of the innate immune system including neutrophils and on cells mediating the connection of innate and adaptive immune system such as plasmacytoid dendritic cells (22). In line with the importance of PDE4 on the regulation of a wide variety of cell types and cytokines, apremilast affects a number of cytokines. It can reduce production of both Th1 and Th17 cytokines (23). In addition, it influences the cytokines that are considered to be important mediators of the crosstalk between innate and adaptive immune functions: TNFα, IL-1 and interferons (22-24). For example, apremilast has been shown to increase levels of the anti-inflammatory IL1 receptor antagonist alpha in patients with psoriatic arthritis treated with apremilast, while it reduced concentration of monocyte chemoattractant protein-1 (MCP-1) (also called chemokine (C-C motif) ligand 2 (CCL2)) (23). Interestingly, C-C chemokine receptor type 2 (CCR2), a receptor of CCL2 on neutrophils, has recently been shown to be crucial in the recruitment of neutrophils into joints in rheumatoid arthritis (25).

This wide spectrum of antiinflammatory actions of apremilast might be important in the therapy of PPP. PPP is characterized by a strong inflammation in lesional skin, in which both the innate and adaptive immune systems are represented (26). While PPP has great similarities in the cytokine profiles compared to plaque-type psoriasis, including overexpression of IL17 and TNFα (26;27), neutrophils are more prominent both clinically (pustules) and in histopathology in PPP compared to plaque-type psoriasis.

Apremilast has already proven to be effective in the treatment of plaque-type psoriasis and psoriatic arthritis, and in a sub-analysis also in palmoplantar involvement of plaque-psoriasis

(28). Given the wide overlap of clinical, immunological and histological features of PPP and plaque-type psoriasis in conjunction with the observation that apremilast also effectively targets the innate immune system (e.g. neutrophils) it may be speculated that apremilast can successfully be used in the treatment of PPP.

The planned study is a multicenter, open label, single-arm pilot study intended to gain information on safety, clinical efficacy and the mechanistical effects of apremilast on PPP.

6.2 Potential Risks and Benefits

According to the 'summary of the risk management plan (RMP) for Otezla® (apremilast)' (29), by blocking the action of PDE4, apremilast reduces the symptoms of psoriasis and psoriasis arthritis. Because of exclusion of patients with moderate / severe kidney disorders, liver disorders, children and pregnant or breastfeeding patients from clinical trials, there is no information on safety or effectiveness of Otezla® for these patients. However, these patient groups will also be excluded for the clinical study presented here.

Important identified risks include:

- weight decrease in patients with Body Mass Index (BMI) <20 kg/m^2
- depression

Important potential risks include:

- inflammation of blood vessels (vasculitis)
- risk of triggering suicide (suicidal thoughts)
- tumors (malignancies)
- nervousness and anxiety
- serious infections
- major heart problems (major adverse cardiac events [MACE] and tachyarrhythmia)
- effects on the developing child if used during pregnancy

For more detailed information on these identified and potential risks please refer to the 'summary of the risk management plan (RMP) for Otezla® (apremilast)' (29) and the 'Rote Hand Brief' (30).

Otezla® has been approved for the treatment of patients with moderate to severe plaque psoriasis and for the treatment of patients with active psoriatic arthritis. Overall, no serious safety issues are associated with Otezla® and the benefit-risk profile for Otezla® is acceptable and the risks can be mitigated though professional labeling.

7 Study Objectives and Purpose

7.1 Primary Objective

The primary objective of this study is:

- To demonstrate a significant improvement of PPPASI at week 20 compared with baseline in moderate to severe chronic palmoplantar pustulosis under apremilast therapy.

7.2 Secondary Objective(s)

The secondary objectives of the study are:

- To evaluate an improvement of PPPASI at all assessment times compared with baseline in moderate to severe chronic palmoplantar pustulosis under apremilast therapy.
- To evaluate differences during the treatment with apremilast in life quality assessment measures: Dermatology Life Quality Index (DLQI) at all assessment times compared with baseline
- To evaluate safety of apremilast in patients with moderate to severe palmoplantar pustulosis

Exploratory objectives are:

- Time course of Hand and Feet Physician Global Assessment (H&F PGA) at all assessment times.
- Pustules count 50 response and Pustules count 75 response, defined as a 50% and 75% decrease in Pustules count from baseline, during the 20 weeks treatment period
- To evaluate differences in the mean change from baseline at all assessment times of VAS pruritus / itch, VAS discomfort / pain at all assessment times relatively to day 0 (baseline)
- To evaluate changes in Psoriasis Area Severity Index (PASI), Physician Global Assessment (PGA) and dynamic H&F PGA if plaque psoriasis is present between baseline and all assessment times
- To explore the effect of apremilast on immunological markers in serum / plasma
- To explore the effect of apremilast on immunological markers in skin biopsies (sub-study, see Section 12.1.10.2)

8 Study Design

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the ICH E6 guideline 'Note for Good Clinical Practice' (CPMP/ICH/135/95) (2) based on the principles of the Declaration of Helsinki (3). The study will be duly conducted in compliance with the Medicinal Products Act (Arzneimittelgesetz AMG), (§§ 40-42) (1). An independent ethics committee and the competent authority must review and approve the study before any patients are enrolled.

8.1 Description of the Study Design

This is a multicenter, open-label, single-arm, phase II, pilot study to evaluate the efficacy and safety of apremilast involving approximately 20 patients with PPP. The screening period is up to 4 weeks and treatment takes place over 20 weeks per patient. No follow up period takes place. No extension is planned.

Recruitment period is 4 months; hence study duration from FPI to LPO is approx. 9 months. 4 patients per site are expected to be recruited, assuming enrolment of both genders with distribution according to prevalence of condition. If recruitment is not running as anticipated after 2 months, recruitment will be opened to become competitive.

Patient recruitment will take place at approximately 5 sites in Germany. The investigators should have relevant expertise in diagnosing and treating PPP or be specialized in dermatology. Patients will be enrolled until 20 patients are included into the study. Drop-outs will not be replaced.

Please refer to the Study Flow Chart in the synopsis for the time schedule of the assessments.

Five visits per patients are planned including:

Visit 1 at week -4 - -1 (screening)

Visit 2 at week 0 (baseline)

Visit 3 at week 4

Visit 4 at week 12

Visit 5 at week 20 (end of study)

After completion of participation in the study, patients are advised to follow medical management of their treating physician (see as well Section 10.6.1).

8.2 Study Endpoints

8.2.1 Primary Endpoint(s)

- Percentage change from baseline in PPPASI after 20 weeks of treatment with apremilast

8.2.2 Secondary Endpoint(s)

- Absolute and percent change from baseline in PPPASI during the 20 weeks treatment period

- PPPASI 50 response and PPPASI 75 response, defined as a 50% and 75% decrease in PPPASI from baseline, during the 20 weeks treatment period
- DLQI bands (0-1 no effect, 2-5 small effect, 6-10 moderate effect, 11-20 very large effect, 21-30 extremely large effect) during the 20 weeks treatment period
- Absolute and percent change from baseline in DLQI during the 20 weeks treatment period
- Safety as assessed by treatment-emergent adverse events (TEAEs), vital signs and physical examination

8.2.3 Exploratory Endpoints

- Absolute and percentage change from baseline in level of immunological markers in plasma / serum during the 20 weeks treatment period with apremilast
- Percentage change from baseline in level of immunological markers in skin biopsy samples after 20 weeks of treatment with apremilast (sub-study)

8.3 Patient Identification

Patients will be identified from the investigator's database.

Upon enrolment, each patient will receive a 5 digit patient number (XX-XXX) starting with:

- 2 digits for the site
- separated by hyphen
- 3 digits for the patient (ascending order)
- E.g. 01-001

Within each site, the investigator will allocate the patient numbers in ascending order of patients screened and include each screened patient in a screening, enrolment and randomization log with site number, a running patient number and year of birth. All patients will be identified by the unique patient number in a patient identification log in the investigator site file.

As this study is an open label, single-arm study no randomization will take place.

Patients who drop out will not be replaced.

8.4 Withdrawal of Patients

In accordance with the informed consent and the Declaration of Helsinki (3), any patient can refuse to participate or withdraw from the study without giving reasons at any time without any penalty or loss of benefits to which the patient is otherwise entitled. When appropriate, patients may be placed on other conventional therapy when clinically indicated.

Patients have to be withdrawn from the study by the investigator if at least one of the following events occurs

- Withdrawal of informed consent
- Pregnancy

- Any study medication discontinuation or dose reduction during the up-titration (days 1 to 6)
- Study medication discontinuation (i.e. no study medication taken) during the maintenance phase irrespective of the reason for more than 5 days in a row or a total of 10 days, or dose reduction (i.e. ≤1 tablet per day) during the maintenance phase (from day 6 onwards) irrespective of the reason for more than 5 days in a row or a total of 10 days
- Major protocol violation (e.g. patient requires the use of medication and / or treatments not permitted by the study protocol)
- Severe treatment emergent adverse events that in the opinion of the investigator results in a risk / benefit assessment with negative results
- Patients are also to be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason
- Depression worsening under treatment

Patients are to be considered withdrawn if they state an intention to withdraw, fail to return for visits, become lost to follow up for any other reason, or if any of the following occur: discovery of patient ineligibility; errors in treatment compliance; missed or incorrect assessments.

Protocol violations do not necessarily lead to the patient's withdrawal unless they constituted a significant risk to the patient's safety. For patients not completing the entire study, all used and unused study drug should be returned by the patients to the defined personnel at the site.

Patients who prematurely withdraw from the study will be scheduled for an end-of-study visit as soon as possible (11.2.6). An end-of-study page will be completed, giving the date and primary reason for stopping treatment if provided. Patients prematurely withdrawn from the study will not be replaced. Patients who prematurely withdraw from the study for any reason at any time are excluded from the continuation of the study and will be treated if indicated as for any event still ongoing at the end of a clinical study according to standard practice under supervision by an experienced dermatologist or will be referred to a dermatologic practice for further treatment according to standard practice. In the case of premature discontinuation due to an adverse event (AE), the investigator should ensure that the patient receives a suitable therapy appropriate to his / her conditions.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show due diligence by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

8.5 Discontinuation of Entire Study

The study must be terminated prematurely for the following reason(s):

- Updated risk / benefit assessment with negative results (sponsors' and coordinating investigators' assessment)
- Study cannot be completed within a reasonable time frame due to slow patient recruitment

The regulatory authorities and the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) must be notified of premature termination of the study. The investigator may

be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the patient's interests.

In addition, a site may be discontinued at any time by the sponsor and all study materials removed. Possible reasons for termination of the study at the site include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrolment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

9 Selection of Patients

9.1 Inclusion / Exclusion Criteria

The investigator must ensure that all patients who meet the following inclusion and exclusion criteria are offered enrolment in the study. Patients will be enrolled if all inclusion and none of the exclusion criteria are met. All patients screened to participate in the study will be documented and the reason for study exclusion will be documented to avoid enrolment bias.

9.1.1 Inclusion Criteria

- Male and female patients aged 18 years or more at screening visit.
- Patients with chronic PPP (disease history of at least 6 months of diagnosis), who are eligible for treatment with systemic therapy defined as having PPP inadequately controlled by topical treatment and / or phototherapy and / or previous systemic therapy
- Patients with chronic moderate to severe PPP defined as patients with a PPPASI ≥ 12 with or without concomitant plaque-type psoriasis
- Negative result of a urine pregnancy test taken at screening and at baseline for all women, except those who are surgically sterile or at least 1 year postmenopausal (i.e. at least 12 consecutive months with amenorrhea without other known or suspected medical cause)
- Willingness and capability of using a highly effective contraceptive measures from Screening visit until the end of at least one menstrual cycle (but not less than 28 days) following discontinuation of apremilast as defined below:
    - Female patient of childbearing potential (fertile, following menarche and until becoming post-menopausal unless permanently sterile) using a highly effective method of contraception OR female patients of non-childbearing potential (surgically sterilized [e.g. hysterectomy, bilateral salpingectomy and bilateral oophorectomy] or post-menopausal)
    - Male patient, and their female partner of childbearing potential, using a highly effective method of contraception
    - Adequate contraceptive method defined as:
        - A method with less than 1% failure rate (e.g. permanent sterilization, hormone implants, hormone injections, some intrauterine devices, or vasectomized partner)

        OR

        - The use of two methods of contraception (e.g. one barrier method [condom, diaphragm or cervical/vault caps] with spermicide and one hormonal contraceptive [e.g. combined oral contraceptives, patch, vaginal ring, injectables and implants])
- Patient is capable of understanding and giving written, voluntary informed consent before study screening.
- Willingness and capability of complying with all study procedure requirements, as per the Investigator's judgment (e.g. patient able to swallow the apremilast tablets, blood sampling).

9.1.2 Exclusion Criteria

General

- Pregnant or breast-feeding women.
- Current or history of psychiatric disease that would interfere with the ability to comply with the study protocol or give informed consent.
- Patients known to have had a substance abuse (drug or alcohol) problem within the previous 12 month
- Individuals who are involved in the organization of the study
- Patients who are in any way dependent on the investigator
- Patients who are participating in a clinical study
- Relatives, partner or staff of any clinical site personnel

Disease-related

- Evidence of skin conditions (e.g. eczema) other than PPP / psoriasis that would interfere with evaluations of the effect of study medication on PPP or psoriasis.
- Laboratory values from routine blood test taken within the 8 weeks prior to screening with any of the following:
    - Serum creatinine >1.4 x upper limit of normal (ULN) for age and gender
    - Estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m^2 according to the CKD-EPI equation
- Pustular psoriasis lesions on the part of body other than hands or feet
- Significant concurrent medical conditions at the time of screening, including:
    - Risk factors for renal toxicity (renal inflammation)
    - Severe hepatic dysfunction
    - Unstable angina pectoris
    - Uncompensated congestive heart failure
    - Severe pulmonary disease requiring hospitalization or supplemental oxygen therapy
    - Immunodeficiency disorders: primary or secondary
    - Known positive HIV test result, hepatitis B surface (HBS) antigen or hepatitis C (HCV) test result
    - Uncontrolled Insulin-dependent diabetes mellitus
    - Cancer or history of cancer (except for resected cutaneous basal cell or squamous cell carcinoma) in the last 5 years
    - Open cutaneous ulcers
- Any condition that, in the judgment of the investigator, might cause this study to be detrimental to the patient.

Medication-related

- Ultraviolet B (UVB) therapy, topical steroids, topical calcineurin inhibitors, topical Vitamin A or D analog preparations, or anthralin within 14 days of baseline

  Exceptions: low potency topical corticosteroids (class I and II, according to European classification for potency of topical corticosteroids) will be allowed as therapy for the face, groin, axillae in accordance with the manufacturer's suggested usage dose
- Psoralen plus ultraviolet A radiation (PUVA), ciclosporin, acitretin, alitretinoin, alefacept (Amevive®), anakinra (Kineret®), systemic corticosteroids, methotrexate, fumaric acids or any other systemic anti-psoriasis therapy within 28 days of baseline
- Prior (within the last 2 years) or concomitant use of antipsoriatic biologic therapy with TNF-alpha blocker and / or ustekinumab and / or ixekizumab and / or secukinumab and / or brodalumab and / or guselkumab
- Concomitant use of strong cytochrome P450 3A4 (CYP3A4) enzyme inductors (e.g. rifampicin, phenobarbital, carbamazepin, phenytoin and St. John`s wort)
- Use of an investigational drug within 4 weeks prior to baseline or 5 pharmacokinetic / pharmacodynamics half-lives (whichever is longer)
- Prior treatment with apremilast / Otezla®
- Receipt of any live (attenuated) vaccine within 28 days prior to baseline
- Concomitant use of any other PDE4 inhibitor
- Patients with are hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption
- For patients with skin biopsy samples taken: patients with clinically relevant coagulation disorders or medication or known hypersensitivity against local anesthetics

10 Study Medication

10.1 Investigational and Control Drugs

The investigational product apremilast is manufactured, packaged and supplied by Celgene Europe Ltd. Table 1 gives an overview of the pharmaceutical information. For labelling refer to Section 10.3.

Table 1: Pharmaceutical information

Formulation	
Appearance	The Otezla 10 mg film-coated tablet is a pink, diamond shaped film-coated tablet with “APR” engraved on one side and “10” on the opposite side. The Otezla 20 mg film-coated tablet is a brown, diamond shaped film-coated tablet with “APR” engraved on one side and “20” on the opposite side. The Otezla 30 mg film-coated tablet is a beige, diamond shaped film-coated tablet with “APR” engraved on one side and “30” on the opposite side.
Active ingredient / concentration	apremilast 10 / 20 / 30 mg
Additional ingredients	tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate film-coating: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide red (E172) 20 mg film-coated tablet also contains iron oxide yellow (E172), 30 mg film-coated tablet also contains iron oxide yellow (E172) and iron oxide black (E172)

10.2 Route of Administration, Dosage, Dosage Regimen and Treatment Period

Apremilast will be taken orally twice daily (except day 1). Patients will receive tablets in a blister/bottles sufficient for one month. To mitigate potential gastrointestinal side effects (primarily mild-to-moderate nausea and diarrhea), dose titration will be implemented in this study in accordance with the treatment guideline for Psoriasis and Psoriasis Arthritis given in the SmPC (31). A titration pack will include tablets of 10, 20 and 30 mg for a period of one month. During the first 1 to 5 days, the dosage will be up-titrated (Table 2). From day 6 onwards, patients will receive the 30 mg BID dose. Subsequent packs include only tablets of 30 mg strength.

Table 2: Dosing information

Day	Morning Dose	Evening Dose	Total Daily Dose
1	10 mg (pink)	-	10 mg

Day	Morning Dose	Evening Dose	Total Daily Dose
2	10 mg (pink)	10 mg (pink)	20 mg
3	10 mg (pink)	20 mg (brown)	30 mg
4	20 mg (brown)	20 mg (brown)	40 mg
5	20 mg (brown)	30 mg (beige)	50 mg
6 onwards	30 mg (beige)	30 mg (beige)	60 mg

10.3 Packaging and Labelling

Medication labels will comply with the legal requirements (Directive 2003/15/EC Art. 15, AMG § 10 section 10 and GCP-V § 5).

10.4 Storage of Study Medication

Until dispensed to the patients, study medication will be stored in a securely locked area, accessible to authorized personnel only.

Apremilast should not be stored above 30°C; under this condition, it is stable for 21 months.

10.5 Study Medication Supply and Re-supply, Accountability Procedures

The study sites will be supplied by the sponsor or its designee with sufficient study medication. Study medication must be received by a designated person at the investigation site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated personnel has access.

All study drug sent to the investigator will be accounted for and in no case used in any unauthorized situation. They are to be dispensed only in accordance with the protocol.

Upon receipt, all study medication should be stored according to the instructions specified on the drug labels (section 10.3). Trained study personnel at each site will be responsible for dispensing / taking back the study medication to / from the patient. Each patient will receive sufficient study medication at the study visit indicated in the flow chart (see also Section 10.6).

Used (empty), partially-used and unused study medication must be returned to the investigation site at the end of the study (visit 5 or early termination) at the latest. Study medication will not be provided once patients have completed or discontinued the study.

The investigator must maintain an accurate record of the shipment and dispensing of study medication in a drug accountability form. All medication will be counted before dispensing and after returning. The site monitor will perform monitoring of drug accountability during site visits and at the completion of the study before database lock. At the conclusion of the study and as appropriate during the course of the study, the site monitor will collect or the investigator will return all used and unused study medication, packaging, drug labels, and a copy of the

completed drug accountability form to the sponsor or its designee provided in the investigator site folder at each site. The returned study medication will be destroyed.

10.6 Instructions for Supplying and Taking the Study Medication

At visit 2, patients will receive a starter pack containing tablets of 10, 20 and 30 mg strength.

During the first 1 to 5 days, the dosage will be up-titrated according to Table 2. From day 6 onwards, patients will receive the 30 mg BID dose. Study medication shall be taken as described in section 10.2 (i.e. according to SmPC(31)).

As applicable, bottles with tablets of 30 mg strength will be handed out at visits to cover the study period between visits.

At visits 3, 4 and 5 patients are requested to bring back their used medication (empty and filled blisters/bottles) to site for checking the drug accountability.

At each visit (except screening and V5 / End of study) the patient will be reminded how to take the study medication.

10.6.1 Treatment after End of Study

After the end of study participation the investigator will ensure that the patient receives a suitable therapy appropriate to patient's condition (see as well Section 8.1).

10.7 Permitted Study Medication Dose Adjustments and Interruptions

For patients who are unable to tolerate the protocol-specified dosing scheme, the following interruptions and / or dose adjustments are permitted:

At the discretion of the investigator treatment may be interrupted during the maintenance phase for a maximum of 5 days in a row or a total of 10 days (see also Section 8.4). In addition, a reduction of the dose from day 6 onwards (only during the maintenance phase) is allowed: the dose may be reduced to one tablet (30 mg) per day for a maximum of 5 days in a row or a total of 10 days. All interruptions and adjustments of study treatment must be recorded in the Case Report Form (CRF).

Patients who experience any uncomfortable event should contact the investigator to assess the need for safety assessments (AEs and SAEs). In case of any AE a discontinuation may be decided by the principal investigator.

AEs and SAEs will be recorded in the corresponding AE page of the CRF. In case of a SAE, a SAE form is to be completed (see also Section 13.3). If the patient does not prematurely discontinue the study, the next regular scheduled visit should be performed as planned. If the patient does prematurely discontinue the study at a visit on site, this visit should be considered as the end-of-study visit.

10.8 Prior and Concomitant Treatment

All prior (taken within 3 month before study start) and concomitant therapies (drugs, such as prescription, over-the-counter, birth control pills etc., and non-drug therapies) will be recorded in the CRF. Other key medications and therapies, including previous treatment for tuberculosis or relevant diseases, should be recorded.

All medications and therapies for psoriasis, including systemic and topical medications (topical only those taken within the last three months, see Section 12.3.3) and all medications for psoriatic arthritis should also be recorded, including the stop dates for medications and therapies prohibited in the study. Responses to prior psoriasis therapies should be recorded.

10.8.1 Permitted Treatments

Concomitant medication (except those listed under exclusion criteria, Section 9.1.2) required for the treatment of concomitant diseases and not known to interfere with the study drug or to mask the effect of the study drug, is unrestricted and may be continued during the study.

Low potency topical corticosteroids (class I and II, according to European classification for potency of topical corticosteroids) will be allowed as background therapy for the treatment of the face, axillae, and groin in accordance with the manufacturer's suggested usage during the course of the study except for lesions selected for clinical evaluations.

An unmedicated skin moisturizer (without urea) is permitted for body lesions only. Patients should not use the unmedicated skin moisturizer within 12 hours prior to the clinic visit on lesions selected for clinical evaluations.

After consultation with Investigators, the Sponsor will provide a list of concomitant medication for background therapy (low potency topical corticosteroids or unmedicated skin moisturizers) in a separate document. Due to the wide availability of moisturizing products, this list will be periodically updated based on feedback during the study from Investigators.

10.8.2 Prohibited Treatments

For prohibited prior and concomitant treatments please refer to the medication-related exclusion criteria (Section 9.1.2).

10.9 Procedures for Monitoring Compliance

The investigator should promote compliance by instructing the patient to apply the study drug exactly as prescribed and by emphasizing that compliance is necessary for the patient's safety and the validity of the study. The patient will be instructed how to apply the medication and to contact the investigator if he is unable for any reason to apply the study drug as prescribed. The study medication will be dispensed as indicated in the flow chart. Patients will be instructed to return all used and unused medication containers during and at the end of the study. Documentation also includes: medication not returned because it was taken / used and medication not returned because of other reasons (e.g. medication lost). Compliance with the treatment assignments will be controlled by the investigator and the study site personnel at every visit. Patients will be questioned regarding irregularities in terms of application since the last visit (e.g. missing doses, overdoses, failures in the application technique, frequency of application). Any kinds of irregularities are documented in the CRF. All CRFs are monitored by a site monitor for compliance with the protocol.

Celgene will inform the sponsor on any annual IB or SmPC update becoming available and will supply the sponsor with the document for distribution to the respective study PIs/ Investigators

11 Study Schedule

11.1 Study Flow Chart

Please refer to Study Flow Chart in the synopsis. The flow chart lists all of the assessments and indicates with an 'X' the visits at which they will be performed.

11.2 Study Visit Description

11.2.1 Visit 1 - (Screening / Day -28 - -1)

- The investigator informs the patient about the study and obtains the informed consent form (ICF). The form must be dated and signed by both the patient and the investigator. One signed original will be provided to the patient.
- After informed consent form is signed a patient identification number will be assigned to the patient.
- Inclusion and exclusion criteria for entry into the study will be verified
- PPPASI will be assessed (must be ≥ 12 for inclusion).
- A urine pregnancy test (β-hCG) will be performed in females with childbearing potential.
- Demography and educational status will be documented.
- Medical and psoriasis history and prior medication will be documented.
- Psoriasis Arthritis (PsA, present Yes / No) and comorbidity will be documented.
- Concomitant medication will be documented.
- The patient will be interviewed concerning the occurrence of SAEs.
- Nicotine anamnesis will be documented.
- Physical examination including weight and height (BMI) and vital signs will be assessed.
- Routine blood test / urinalysis must be available within the ranges given in the exclusion criteria not older than 8 weeks prior to screening.
- A return appointment for the baseline visit will be scheduled (maximum 28 days after screening).

11.2.2 Visit 2 - (Baseline / Day 0)

- Inclusion and exclusion criteria for entry into the study will be verified.
- A urine pregnancy test (β-hCG) will be performed in females with childbearing potential.
- Physical examination including weight and vital signs will be assessed.
- PsA and comorbidity will be documented.
- Concomitant medication will be documented.
- The patient will be interviewed concerning the occurrence of SAEs.

- Serum and plasma samples will be taken.
- The investigator will
    - ask the patient to rate their pruritus and pain on hands and feet using the VAS and to fill in the DLQI questionnaire.
    - assess the PASI, PPPASI, PGA, H&F PGA and pustules count.
- The study medication will be dispensed and patients instructed how to take the study medication.
- The patient will be instructed to return all study medication to the next visit.
- Photographs will be taken (optional).
- Biopsies will be taken (two lesional biopsies from feet or hands). The taking of biopsies is optional.
- A return appointment for the next visit will be scheduled.

11.2.3 Visit 3 - (Week 4, Day 28 ±4)

- A urine pregnancy test (β-hCG) will be performed in females with childbearing potential.
- Vital signs will be assessed.
- Concomitant medication will be documented.
- The patient will be interviewed concerning the occurrence of AEs.
- Serum and plasma samples will be taken.
- The investigator will
    - ask the patient to rate their pruritus and pain on hands and feet using the VAS.
    - assess the PASI, PPPASI, PGA, H&F PGA, dynamic H&F PGA and pustules count.
- Study medication will be collected for drug accountability and documentation for treatment compliance. Further study medication will be dispensed. The patient will be reminded and re-instructed on when and how to take the study medication.
- The patient will be instructed to return all study medication to the next visit.
- A return appointment for the next visit will be scheduled.

11.2.4 Visit 4 - (Week 12, Day 84 ±4)

- A urine pregnancy test (β-hCG) will be performed in females with childbearing potential.
- Vital signs will be assessed.
- PsA and comorbiditiy will be documented.
- Concomitant medication will be documented.
- The patient will be interviewed concerning the occurrence of AEs.
- Serum and plasma samples will be taken.

- The investigator will
    - ask the patient to rate their pruritus and pain on hands and feet using the VAS and to fill in the DLQI questionnaire.
    - assess the PASI, PPPASI, PGA, H&F PGA, dynamic H&F PGA and pustules count.
- Study medication will be collected for drug accountability and documentation for treatment compliance. Further study medication will be dispensed. The patient will be reminded and re-instructed on when and how to take the study medication.
- The patient will be instructed to return all study medication to the next visit.
- A return appointment for the next visit will be scheduled.

11.2.5 Visit 5 - (Week 20, Day 140 ±7)

- A urine pregnancy test (β-hCG) will be performed in females with childbearing potential.
- Nicotine anamnesis will be documented.
- Physical examination including weight and vital signs will be assessed.
- PsA and comorbidity will be documented.
- Concomitant medication will be documented.
- The patient will be interviewed concerning the occurrence of AEs.
- Serum and plasma samples will be taken.
- The investigator will
    - ask the patient to rate their pruritus and pain on hands and feet using the VAS and to fill in the DLQI questionnaire.
    - assess the PASI, PPPASI, PGA, H&F PGA, dynamic H&F PGA and pustules count.
- Study medication will be collected for drug accountability and documentation for treatment compliance.
- Photographs will be taken (optional).
- Biopsies will be taken (two lesional biopsies from feet or hands). The taking of biopsies is optional.

11.2.6 Early Termination Visit

In case of early termination of a patient, effort will be made to schedule an early termination visit and assess the following, if possible:

- The reason for discontinuation will be documented.
- A urine pregnancy test (β-hCG) will be performed in females with childbearing potential.
- Physical examination including weight and vital signs will be assessed.
- PsA and comorbidity will be documented.
- Concomitant medication will be documented.

- The patient will be interviewed concerning the occurrence of AEs.
- Serum and plasma samples will be taken.
- Biopsies will be taken (two lesional biopsies from feet or hands). The taking of biopsies is optional.
- The investigator will
    - ask the patient to rate their pruritus and pain on hands and feet using the VAS.
    - assess the PASI, PPPASI, PGA, H&F PGA, dynamic H&F PGA and pustules count.
- Study medication will be collected for drug accountability and documentation for treatment compliance.

11.2.7 Unscheduled Visits

Due to clinically significant reasons additional visits can be required. Parameters examined at these visits should be documented in a similar way as with all other visits (e.g. patent file and CRF).

12 Assessments

Every effort should be made to ensure that the investigator who performs the assessments for a patient at screening should also perform the assessments for the patient at all subsequent visits. For timing of the assessments please refer to the flow chart in the synopsis or study visit description (11.2).

12.1 Efficacy Assessments

12.1.1 Dermatology Life Quality Index (DLQI)

The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of a disease on the patient's daily life (32). It is a 10-item questionnaire and can be used to assess 6 different aspects: symptoms and feelings, leisure, daily activities, work or school performance, personal relationship and treatment. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life was impaired. The DLQI could also be expressed as a percentage of the maximum possible score of 30.

For further details see Appendix 21.1.

12.1.2 Psoriasis Area and Severity Index (PASI)

The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. The PASI is a validated instrument that has become standard in clinical trials for psoriasis.

PASI scores range from 0 to 72, with higher scores reflecting greater disease severity (33). Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score.

For more details refer to Appendix 21.2.

12.1.3 Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI)

The PPPASI will assess palms of hands and soles of feet for psoriasis involvement.

For more details refer to Appendix 21.3.

12.1.4 Physician's Global Assessment (PGA)

The PGA describes the severity of psoriasis using 5 categories.

For more details refer to Appendix 21.4.

12.1.5 Dynamic Hand and Feet (H&F) Physician's Global Assessment

The dynamic H&F PGA describes the global improvement compared with baseline. It relies on the physician's memory of the baseline severity to evaluate the level of alteration.

For more details refer to Appendix 21.5.

12.1.6 Hand and Feet (H&F) Physician's Global Assessment

The H&F PGA describes the severity of psoriasis on the hands and / or feet using 5 categories.

For more details refer to Appendix 21.6.

12.1.7 Pustules Count

A pustule count of both hands and feet to assess the response with regard to pustular lesions will be performed (total pustules count).

To be included in the count, pustules must be macroscopically visible, white / yellow/brown in color, with or without crust, and present on the glabrous skin of the palms and / or soles.

12.1.8 Visual Analogue Scale (VAS)

A VAS is used to assess pruritus (itch) and discomfort / pain on hands and feet.

The patient will be asked to place a vertical stroke on a 100 mm VAS on which the left-hand boundary represents either no pruritus (itch) or discomfort / pain, and the right-hand boundary represents either pruritus (itch) or discomfort / pain as severe as can be imagined. The distance from the mark to the left-hand boundary will be recorded.

For more details refer to Appendix 21.7.

12.1.9 Photo Documentation

Optional, high-quality, color, digital photographs of the hands (dorsum and palm) and / or feet will be obtained at baseline (visit 2) and at the end of the study at visit 5 (week 20) have given their consent for taking photographs before study start. Photographs will not be formally standardized and therefore will not be used to evaluate efficacy and are intended for visual comparison only.

Photographs will be taken with any suitable device. An exemplary photograph will be provided at the beginning of the study for guidance of the right field of view. The photographs will be identified with:

- Study Number (069-008)
- Patient's Identification number
- Date (YYYYMMDD)
- Visit number (VX);
- View (left / right hand (dorsum / palm), left / right foot));

- Example: 069-008_XX-XXX_20170413_V2_left hand palm.

As appropriate, pictures must be modified to retain the patient's anonymity. Pictures will be provided on a memory stick or CD-ROM to the sponsor.

12.1.10 Exploratory assessments

Samples will be shipped to the Psoriasis Research and Treatment Center (PRTC, Department of Dermatology and Allergy and Institute of Medical Immunology, Charité - Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany). The person responsible will be Dr. Robert Sabat in consultation with the sponsor. Instructions for the preparation and shipping will be provided separately. This exploratory analysis will be performed by the PRTC or companies / scientific group working with PRTC.

These samples may be banked for future use (e.g. validation of markers identified in future studies) that will enable further research on the described analyses once new scientific knowledge is generated. Thus, the samples will be retained for no longer than 10 years after study completion.

The results of the exploratory assessments are not applicable for clinical decision-making or patient management; therefore the investigators will not be informed of individual results. Aggregate data will be used in scientific publications or presented at medical conventions. Exploratory research / validation studies data will be published or presented only in a way that does not identify any individual patient.

12.1.10.1 Serum / plasma immunological marker analysis

Serum / plasma samples will be collected to explore the effect of apremilast on levels of immunological markers and/or PPP-specific alterations. The analyses of markers in blood may include, but are not be limited to, the quantification by enzyme-linked immunosorbent assays (ELISA) of concentrations of markers in serum or plasma such as (i) IL-22, (ii) β-defensin 2, and / or (iii) sP-selectin.

For these analyses samples (27 ml per time point: 9 ml serum tubes, 9 ml EDTA tubes, 9 ml Lithium-Heparin tubes) will be taken at the following time points: baseline (before treatment) and after 4, 12 and 20 weeks of treatment.

12.1.10.2 Skin biopsy immunological marker sub-study

Skin biopsy samples will be collected in an optional (voluntary) exploratory sub-study to explore the effect of apremilast on levels of immunological markers in skin and/or PPP-specific alterations (separate Informed Consent Form will need to be completed by consenting patients). Details on this sub-study, which will be performed separately from the main study by Dr. Sabat (PRTC) and colleagues, will be outlined in a separate document and will not be included in the Clinical Study Report.

Skin markers

The analyses of skin markers may include, but are not be limited to, (i) total transcriptome analysis, (ii) specific messenger ribonucleic acid (mRNA) quantification, and / or (iii) immunohistochemistry.

Total transcriptome analysis

mRNA expression of lesional skin will be analyzed by total mRNA sequencing. Respective skin biopsy samples (2 lesional 4 mm biopsies) will be taken at baseline (before treatment) and after 20 weeks of treatment.

Specific mRNA quantification

The mRNA expression of markers, such as e.g. IL-23 p19, IL-17A, CXCL (CXC Motif Chemokine) 8, β-defensin 2, will be individually quantified by real-time polymerase chain reaction on reverse transcribed mRNA (qPCR) lesional skin.

Samples will be taken at the following time points: baseline (before treatment) and after 20 weeks of treatment.

Immunohistochemistry

The number of immune cells, such as T cells will be quantified by immunohistochemistry of lesional skin.

Samples will be taken at the following time points: baseline (before treatment) and after 20 weeks of treatment.

12.2 Safety Assessments

12.2.1 Adverse Events (AE)

The investigator will assess and record any AEs (for definition, see Section 13.1) starting from baseline in detail including the date of onset, intensity, relationship of the AE to study drug, action(s) taken, seriousness, time course, duration and outcome. All AEs with onset from visit 2 are to be reported on the AE page of the CRF with complete information as required (see Section 13.2). If AEs occur, the main concern will be the safety of the study patients. At time of the informed consent signature, each patient must be given the name and phone number of investigation site personnel for reporting AEs and medical emergencies.

12.2.2 Pregnancy Test

A urine pregnancy test will be performed for female patients of childbearing potential at the site at all visits.

12.2.3 Physical Examination and Vital Signs

The physical examination will include the determination of height and weight.

If indicated based on the symptoms or medical history, additional exams will be performed at the discretion of the investigator.

Information for all physical examinations must be included in the source documentation. Significant findings that are present prior to enrolment must be included in the medical history on the CRF. Serious findings made after ICF signature which meet the definition of an SAE must be recorded as SAE.

Evaluation of vital signs will be performed after 10 minutes resting. Assessments should be performed by the same person throughout the study.

Pulse rate and blood pressure will be measured on the same arm on each occasion with the patient sitting. These data will be recorded in the CRF.

Blood pressure (systolic / diastolic) will be measured with a mercury manometer or an automated device (same type of device for all measurements). Normal blood pressure will be defined as a systolic pressure of 90 - 120 mmHg and diastolic pressure of 60 - 80 mmHg. Notable blood pressure will be hypertension (systolic pressure $\geq$140 mmHg and / or diastolic pressure $\geq$90 mmHg) or hypotension (systolic pressure <90 mmHg and / or diastolic pressure <60 mmHg). A blood pressure indicative of prehypertension (systolic pressure 120 - 140 mmHg and / or diastolic pressure 80 - 90 mmHg) will not be regarded as notable according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (34).

A normal pulse rate will be defined as a rate of 60 - 100 beats per minute. Notable pulse rates are a rate above 100 bpm (tachycardia) and under 60 bpm (brachycardia).

Whether action needs to be taken to address notable vital signs will be decided by the investigator, taking into account the overall status of the patient. No specific action is foreseen as part of the study protocol.

12.3 Demographics and Baseline Characteristics

Demographics and Baseline Characteristics consist of those parameters that are assessed only at screening / baseline.

12.3.1 Patient Demography

Patient demography consists of:

- Age at screening
- Height
- Weight
- Race
- Sex
- Educational status

12.3.2 Medical History

The medical history will be obtained by asking the patient or by inspecting his / her medical records.

Any previous diseases within the last 3 months before screening and any concomitant diseases will be documented in the CRF.

12.3.3 Psoriasis History

For the documentation of the psoriasis history, the patient will be asked or his / her medical records will be inspected for:

- Age at first diagnosis of psoriasis
- Prior psoriasis therapies

  Any previous and concomitant topical therapies within the last 3 months before screening will be documented in the CRF. Any systemic psoriasis therapy and phototherapy will be documented in the CRF.
- Reason(s) for therapy discontinuation or change
- Psoriasis arthritis (yes / no; verified diagnosis (i.e. diagnosed by a rheumatologist)
- Involvement of nails (yes / no)
- Involvement of scalp (yes / no)

12.3.4 Nicotine Anamnesis

- Current smoker, past smoker, non-smoker
- For current and past smoker:

  Cigarettes per day

  Years being a smoker (Start date, end date in case of previous smoker)

  Pack per year (cigarettes per day x years being a smoker / 20)

13 Adverse Event Reporting

13.1 Definitions

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR):

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

Unexpected Adverse Drug Reaction:

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., the IB for Otezla®).

Serious adverse event (SAE):

A SAE is any AE that:

- results in death
- is life-threatening (the term 'life-threatening' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.)
- requires in-patient hospitalization or prolongation of existing hospitalization, except of:
  - An overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be handled/ documented as a SAE.
  - Hospitalization, that was planned before inclusion of the patient in the study for elective operations or treatments does not need to be handled/ documented as a SAE.
- results in persistent or significant disability / incapacity (i.e., a substantial disruption in a patient's ability to conduct normal activities of daily living)
- is a congenital anomaly / birth defect
- is an important medical event that, while it may not result in death or be immediately life-threatening or requires / prolongs hospitalization, may jeopardize the patient and / or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

In-patient hospitalization is considered to have occurred if the patient has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. This does not include an emergency room visit or admission to an outpatient facility. Hospitalization for an elective or planned procedure to treat a pre-existing condition is not considered an SAE unless it results in one of the outcomes listed above (but it has to be documented as planned).

13.2 Record of Adverse Events

All AEs from baseline (visit 2, onset of treatment) until the patient's last study visit and all SAEs upon ICF signature (visit 1) until 30 days after the patient has stopped study participation as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to the investigational product will be collected.

AEs / SAEs will be recorded according to the ICH E6 guidelines on an AE page of the CRF. SAEs will be additionally documented on a SAE report form. Documentation includes the following information: description of AEs in detail including the date of onset, stop date, intensity, relationship of the AE to study drug, action(s) taken, seriousness, time course, duration and outcome. There should be an attempt to report a diagnosis rather than signs, symptoms or abnormal laboratory values.

The clinical intensity of an AE is classified as:

Mild: Signs and symptoms which could be easily tolerated and are transient.

Moderate: Causes discomfort and interferes with normal functioning and interrupts the patient's usual activities but is tolerable.

Severe: Affects considerable usual daily activities, prevents the patient from carrying out his / her daily activities.

An AE is considered to be related to the investigational product if a causal relationship between the investigational product and the AE is at least a reasonable possibility (assessed as 'related', 'probable' or 'possible'), i.e. the relationship cannot be ruled out. If an AE is considered not to be related to the investigational product, the degree of causality to the study drug will be described as 'not related'.

All AEs should be treated appropriately. The action(s) taken regarding the AE are classified as follows:

Treatment for event:

- None
- Concomitant medication given or changed (to be specified on concomitant medication form)
- Others

Action taken with study medication:

- Dose not changed
- Dose reduced
- Dose interrupted
- Dose withdrawn

- Dose increased
- Unknown
- Not applicable

The outcome of the AE is classified as follows: recovered / resolved, recovered / resolved with sequelae, not recovered / not resolved, fatal, unknown.

Data pertaining to AEs and SAEs are collected during each study visit through the patient's spontaneous description or through the investigator's inquiry or examination of the patient.

Once an AE is detected it is followed until its resolution or until it is judged to be permanent. An assessment of any changes in intensity, the suspected relationship to the treatment, seriousness, the interventions required to treat it and the outcome is made at each scheduled visit.

Patients will be supplied with a 24-hour hotline telephone number by the study sites that allows them to notify the study staff of any local reactions on the treated area or any other AEs whether or not related to treatment.

13.3 Procedures for Reporting Serious Adverse Events

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see below.

To ensure patient safety, every SAE, regardless of suspected causality/relatedness to study drug, occurring after the patient has provided informed consent until 30 days after the patient has stopped study participation must be reported to the sponsor within 24 hours of learning of its occurrence. The SAE form will be sent to

TFS Drug Safety

safety.tfs@tfscro.com

Fax: +46 46 2801919

The Sponsor or its designee will inform relevant Regulatory Authorities and Ethics Committees;

- Of all relevant information about serious unexpected events suspected to be related to the investigational product suspected to be related to the investigational product that are fatal or life-threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will be subsequently be submitted within an additional eight days.
- Of all other serious unexpected events suspected to be related to the investigational product as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

Any SAEs experienced after this 30-day period have to be reported to the sponsor if the investigator assumes a causal relationship to the treatment.

Recurrent episodes, complications, or progression of the initial SAE have to be reported as follow-up to the original episode, regardless of when the event occurred. This report has to be submitted within 24 hours of the investigator's receiving the follow-up information. An SAE that is considered completely unrelated to a previously-reported one has to be reported separately as a new event.

Information about all SAEs has to be collected and recorded on the SAE report form. The investigator has to assess the relationship to study drug, complete the SAE report form, and send the completed, signed form by fax within 24 hours to the sponsor or its responsible contact person. The telephone and fax number are listed in the investigator site file provided to the study site as well as in the heading of the SAE report form. The original copy of the SAE report form and the fax confirmation sheet must be kept with the CRF documentation at the study site.

Follow-up information has to be sent to the same person, to whom the original SAE report form was sent, using a new SAE report form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information has to specify whether the event is resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

13.4 Pregnancy

Prior to enrolment, all patients must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for a pregnancy.

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female patient of childbearing potential regardless of age or disease state) occurring while the patient is receiving apremilast, or within the time between the end of at least one menstrual cycle (but not less than 28 days) following discontinuation of apremilast, are considered immediately reportable events. The investigational product is to be discontinued immediately.

The female patient may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The investigator will follow the female patient until completion of the pregnancy, and must notify the Sponsor or its designee immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the investigational product should also be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking investigational product should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

If a pregnancy related event is reported in a female partner of a male patient, the investigator should ask if the female partner is willing to share information with the Sponsor or its designee and allow the pregnancy related event to be followed up to completion.

14 Statistics

A Statistical Analysis Plan (SAP) will be written as a separate document to be completed after finalizing the protocol developed during the conduct of the study. The SAP will be finalized prior to database closure.

Any changes to the statistical analyses planned in the protocol will be justified and documented in the SAP if they were decided before database lock. Any changes made to the SAP after the database lock will be documented in the final study report.

Summary statistics for continuous variables will include number (n), mean, standard deviation, median, minimum first quartile, third quartile, and maximum.

Summary statistics for discrete variables will include frequencies and percentages.

If not otherwise specified, p-values will be presented as two-sided p-values and the level of significance is set to 5% (two-sided).

The statistical analysis will be performed using the software SAS version 9.3 or higher.

Exploratory analyses (e.g. inflammatory markers) will not be part of statistical analyses and will be analyzed outside of the study setting.

14.1 Protocol Deviations

Deviations from the protocol including violations of inclusion / exclusion criteria will be assessed as ‘minor’ or ‘major’ on a case by case basis in cooperation with the sponsor. This assessment will take place during a data review meeting, which will take place after the last observation of the last patient and prior to database closure. Major deviations from the protocol will lead to the exclusion of a patient from the per protocol set.

14.2 Analysis Populations

The following two analysis sets are defined in this study:

Full Analysis Set (FAS)

The Full Analysis Set (FAS) is defined as all patients who received at least one dose of study drug.

Per Protocol Set (PP)

The Per Protocol Set (PP) is defined as all patients who received at least one dose of study drug who completed the study with no major protocol violations.

The definition of the PP set will be finalized in the data review meeting prior to database closure.

The FAS and PP will be used for analyses of efficacy endpoints. Since the FAS consists of all patients who received at least one dose of study drug, the FAS will additionally serve as safety analysis set and will be used for analysis of safety endpoints.

14.3 Demographics and Baseline Characteristics

The analyses of patient demographic data will be presented for the FAS and PP. Other baseline characteristics including medical history will be based on the FAS.

Demographics and Baseline Characteristics

Summary statistics will be presented for demographic and baseline characteristic variables. The number and percentage of patients in each category will be presented for categorical variables.

Medical History

Frequency tables for medical history will present the number and percentage of patients per Medical Dictionary for Regulatory Activities (MedDRA), system organ classes (SOC) and preferred terms (PT).

14.4 Treatments

Prior and Concomitant Medications

Frequency tables for prior and concomitant medications will present the number and percentage of patients per Anatomic-Therapeutically-Chemical Code (ATC) class 2 (therapeutic main group) and ATC class 3 (pharmacological sub-group).

Prior medications are defined as medications taken prior to first intake of study drug. Any medication given at least once after the first intake of study drug will be considered as concomitant medication. This means, a medication might be assigned to both, prior and concomitant medications. If no unambiguous assignment to prior and concomitant medication is possible due to incomplete or missing dates, the medication will be assigned to both, prior and concomitant medications.

14.5 Analysis of Primary Endpoint

14.5.1 Primary Endpoint

The primary endpoint is the percentage change from baseline in PPPASI after 20 weeks of treatment with apremilast, defined in 8.2.1.

14.5.2 Statistical Methods of Analysis

The primary endpoint percent change from baseline in PPPASI after 20 weeks of treatment will be summarized as continuous variable together with 95%-confidence limits. Statistical comparison between post- versus pre-treatment values will be done based on the Wilcoxon signed-rank test with two-sided p-value <0.05 indicating significance. Missing values will be replaced using last-observation-carried-forward (LOCF) method for the analysis of the primary endpoint based on the FAS.

The analysis of the primary endpoint will be repeated for the PP set, this analysis will be considered as supportive.

14.6 Analysis of Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints will be based on the FAS and PP set.

Summary statistics will be provided for the secondary efficacy endpoints which are defined as follows:

- Absolute and percent change from baseline in PPPASI during the 20 weeks treatment period
- PPPASI 50 response and PPPASI 75 response, defined as a 50% and 75% decrease in PPPASI from baseline, during the 20 weeks treatment period
- DLQI bands (0-1 no effect, 2-5 small effect, 6-10 moderate effect, 11-20 very large effect, 21-30 extremely large effect on the disease related quality of life) during the 20 weeks treatment period
- Absolute and percent change from baseline in DLQI during the 20 weeks treatment period

All other endpoints except for PPPASI and DLQI are only briefly described within this study protocol: Statistical comparison between post- versus pre-treatment values will be done based on the Wilcoxon signed-rank test with two-sided p-value <0.05 indicating significance.

14.7 Analysis of Secondary Safety Endpoints

All safety evaluations will be performed on the FAS, which consists of all patients who received at least one dose of study drug.

Frequency tables and/or summary statistics will be provided as described below for the secondary safety endpoint which is defined as:

- Safety as assessed by adverse events (AEs), vital signs and physical examination

Adverse Events (AEs)

Treatment emergent AEs (TEAEs) are defined as AEs which started after first intake of study drug. If no unambiguous assignment to treatment emergent is possible due to incomplete or missing dates, the AE will be considered as treatment emergent.

Frequency tables for TEAEs will present the number and percentage of patients per SOC and PT. Frequency tables will also be presented for TEAEs related to study medication, TEAEs leading to study drug discontinuation, serious TEAEs, and serious TEAEs related to study medication. Additional summaries will be provided for TEAEs by intensity.

Vital Signs and Physical Examination

Summary statistics will be provided for each parameter per visit.

14.8 Exploratory Analysis

Exploratory endpoints (plasma / serum immunological marker analysis and the skin biopsy immunological marker sub-study) will be analyzed outside of the study setting by a research laboratory (Psoriasis Research and Treatment Center, University Hospital Charité, Berlin,

Germany). Summary statistics for immunological marker data derived from plasma / serum samples will be incorporated into the results of the Clinical Study Report.

Immunological marker data derived from skin biopsy samples will not be included in the Clinical Study Report.

14.9 Handling of Missing Values

Missing values will be replaced using last-observation-carried-forward (LOCF) method for the analysis of the primary endpoint based on the FAS.

For all other analyses, missing values will not be replaced.

14.10 Examination of Subgroups

No subgroup analyses are planned.

14.11 Sample Size Calculation

This is a pilot study intended to gain first information on the possible clinical and mechanistical effects of apremilast on PPP; therefore the sample size is not based on statistical considerations.

14.12 Interim Analyses

No interim analysis is planned.

14.13 Multiple Comparison / Multiplicity

No formal hypothesis testing will be performed. Any comparison will only be performed exploratory, without adjustment for multiplicity.

15 Data Handling and Record Keeping

15.1 Data Collection

All patient data relevant for the study are captured on paper CRFs. Completed CRFs are checked by the monitor during the periodic monitoring visits according to defined scope. Data reported on the CRF, derived from source documents, have to be consistent with the source documents or the discrepancies should be explained. A source data location list is filed in the investigator site file. Once completeness and correctness has been confirmed by the monitor, the original CRF pages are collected by the monitor. A copy of each CRF remains at the site.

Data Management staff register the CRFs received by monitor in a study-specific tracking register. First CRFs of each site are checked for completeness, accuracy and plausibility.

Subsequently data from the CRFs are entered into the clinical study database by using double data entry method performed by two different individuals. Discrepancies between first and second data entry are resolved by checking the original CRFs, the database will be updated as appropriate. The data entry staff is trained on the study-specific data entry guideline and is supervised by the responsible data manager.

Validation of data is done according to the study-specific data validation plan. Data checks include automatic edit checks within the database as well as data review listings and manual queries performed by data manager or site monitor.

Obvious errors are corrected by data management staff using the self-evident correction list, if available. All other discrepancies are sent to the investigation site for resolution by investigator using a data clarification form. The completed and signed original data clarification forms are sent to data management. The data management updates the database according to the resolved data clarification forms and files these with the CRFs. A copy of the data clarification form is kept with the CRFs at the investigation site.

A database quality control of key safety and efficacy data is performed prior to locking the database. When all queries have been resolved, database quality control has been completed and the analysis populations have been assigned during the blind data review meeting the database will be locked. After database lock the treatment codes will be made available for data analysis.

Any changes to the database after the database has been locked require joint written agreement between clinical project manager, statistician and sponsor.

AEs are coded according to international used MedDRA classification, prior and concomitant medications are coded according to WHO ATC classification**.**

15.2 Source Documentation

All information on CRFs must be traceable to the source documents in the patient's file. All data obtained during this study shall be entered in the CRFs promptly. All source documents from which CRF entries are derived shall be placed in the patient's medical records. In general, the patient's medical records shall be the only source documents.

The original CRFs for each patient will be checked against source documents at the study site by the CRO site monitor.

After review by the site monitor, completed CRFs will be forwarded to Data Management. Instances of missing or uninterpretable data will be discussed with the investigator for resolution.

15.3 Archiving

The investigator must make arrangements to store the essential study documents (as defined in ICH E6, section 8 'Essential Documents for the Conduct of a Clinical Study'(2)) including the investigator site file, until the sponsor or its designee informs the investigator that the documents are no longer to be retained.

The ICH E6 guideline (section 5.5.11) states that essential documents be retained 'until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product'.

In addition, the investigator is responsible for archiving all relevant source documents, patient's files and patient's identification codes for a minimum of 10 years (in Germany according to MBO - (Model) Professional Code for Physicians in Germany and BGB §630e, GCP-V §13).

The sponsor or its designee stores the original CRFs and the above essential documents for at least 15 years (2003/83/EC, section 5.2c) in case the medicinal product and / or the comparator are already on the market, except for source documents pertaining to the individual site, which are kept only by the investigator.

16 Quality Control and Quality Assurance

The study is conducted in compliance with the applicable international and local regulatory requirements as well as applicable ICH E6 guideline(2), the Declaration of Helsinki (3) and in respect of the TFS and / or sponsor Standard Operating Procedures (SOPs) for study preparation, conduct, close out and monitoring.

16.1 Personnel Training

Site monitors and other applicable personnel will be trained prior to the study initiation to familiarize them with the SOPs, the protocol and all study-specific items.

The investigator must ensure that all site staff involved in the conduct of the study is familiar with the protocol and study-specific procedures and have appropriate knowledge of the study drugs. The transfer of duties and a listing of all sub-investigators must be recorded in the investigator site file.

16.2 Clinical Monitoring

The conduct of the study will be closely monitored to verify adherence to ICH E6 guideline(2), AMG (1) and applicable SOPs. An experienced site monitor will advise the investigator during the clinical investigation and will perform the monitoring activities at the site which may include an initiation visit, periodic monitoring visits during the study, and a close-out visit.

At the initiation visit, the site monitor will amongst others review the investigator site file, the protocol and the CRF with the investigator and his / her staff. During the study visit it is the responsibility of the site monitor to secure that the documents required are present in the study documentation according to ICH E6 guideline(2).

Periodic monitoring visits will take place on a regular basis according to a schedule fixed by mutual agreement documented in the monitoring plan. During these visits the site monitor will check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP and the progress of enrolment. The recruitment of patients will be monitored by sending inclusion faxes from site to TFS. Furthermore the site monitor has to ensure the correctness of storage of study drug and will check study drug dispensing and accountability on every visit.

The close-out visit will occur after LPO at the site. The site monitor will collect all required documents, clarify any remaining questions and inform the investigator about the archive requirements of investigator site files including signed informed consent forms, patient identification lists and CRF copies.

The investigator will allow the site monitor to have direct access to all study records, CRFs, corresponding medical records, study drug dispensing records and study drug area and any other documents considered source documentation to confirm their consistency with the CRF entries. All information on CRFs must be traceable to these source documents in the patient's file. Data defined before study start as not requiring a separate written record will be recorded directly in the CRF and are considered source documentation.

TFS monitoring standards require full verification for the presence of informed consent, adherence to the inclusion / exclusion criteria, documentation of AEs / SAEs, medical history according to the monitoring manual and recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

Key study personnel must be available to assist the site monitor during the visit(s). The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information. The investigator must also keep the original ICF signed by the patient (one signed original is given to the patient).

16.3 Audits / Inspections

Audits may be carried out by the sponsor or its designees before, during or after the study. The investigator will permit and assist the sponsor, its designee or responsible government agencies (as required by law) to have direct access to all source data / documents.

17 Ethics

17.1 Regulatory and Ethics Compliance

The study will be conducted in accordance with applicable laws and regulations including, but not limited to, the Medicinal Products Act (Arzneimittelgesetz AMG) (1), the ICH E6 guideline (2) and the ethics principles that have their origins in the Declaration of Helsinki (3). The protocol and the proposed ICFs have been reviewed and approved by a properly-constituted ethics committee before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his / her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, IRBs / IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor or its designee immediately that this request has been made.

17.2 Informed Consent

Informed consent of patients will be obtained in accordance with applicable laws and regulations including, but not limited to, the Medicinal Products Act (Arzneimittelgesetz AMG) and ICH E6 guideline by the investigator and / or his / her sub-investigator(s) personally prior to each inclusion of a patient to the study.

The nature, objective and importance of the study, the possible benefits and disadvantages or risks and the study procedures will be explained to each patient orally and in writing by each investigator and / or his / her sub-investigators personally before the patient is to sign the informed consent. The patients will also be informed

- that their participation is voluntary
- that they are free to withdraw from the study at any time
- that choosing not to participate would not impact on the patient's care or future treatment
- that, by signing the ICF, they explicitly permit access to their personal data relating to study by authorized representatives of the sponsor and the regulatory authorities without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) and / or regulations. The patients will also be informed that their consent for use / analyse their already elevated data may not be revoked by withdrawing from the trial.

Each patient will be given sufficient time to read and discuss the ICF with the investigator and / or his / her sub-investigator(s) in person prior to giving his / her written consent. An oral consent or written consent given via email or fax is not sufficient. Before entry to the study and prior to the conduct of any study-related procedures consent will be recorded by means of the patient's dated signature. The ICF will be signed two times. The patient is then given one (1) original of the information sheet and his / her signed consent form. The other original is filed in the investigator site file at site. The collection of AE information will start at baseline visit.

A separate ICF will be prepared and consent obtained from patients willing to provide skin biopsy samples for the purposes of this study.

17.3 Amendments to the Protocol

Any substantial change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor and, where required, regulatory authorities and the IRB / IEC. Only amendments that are required for patient safety may be implemented prior to IRB / IEC approval.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor or its designee should be notified of this action and the site-specific IRB / IEC should be informed within 10 working days.

17.4 Confidentiality

All involved sites have to confirm that they handle the information available in the documents handed over strictly in confidence.

The process of collecting patient information will comply with the standards for protection of privacy by applicable local / regional / national requirements for patient confidentiality. All records will kept confidential and the patient's name will not be released at any time. Throughout this study all data will not to be released to anyone other than the sponsor / sponsor delegates or representatives of the responsible government agencies, if requested. Caution will be exercised to guarantee patient's confidentiality.

In the event that a potential violation of Data Protection Regulations is detected, the following measures will be implemented: as soon as the situation becomes known immediate action will be taken to remediate the violation and a full investigation will be carried out to identify whether any other subjects are at risk and to ensure appropriate corrective actions are implemented to ensure that the situation does not recur.

18 Financing and Insurance

18.1 Financing

A separate agreement is signed between the CRO on behalf of the sponsor and each investigator / institution containing supplemental information including the financial aspects.

An educational grant is being provided by Celgene GmbH to support the sponsor in carrying out certain of his obligations in relation to this clinical study.

All investigators will sign separate financial disclosure forms, if required by CRO, sponsor, or regulatory authorities.

18.2 Insurance

From the start of the study until its termination each patient will be insured against health impairment occurring as a result of participation in the study in accordance with each national laws and regulations. A copy of the insurance conditions will be handed out to the patient with the informed consent.

19 Publication Policy

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication, especially to public registries at health care bodies (e.g. ClinicalTrials.gov), and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

An integrated Clinical Study Report will be prepared by TFS and reviewed by the sponsor in co-operation with the coordinating investigator. The results from the exploratory sub-studies will not be included in the Clinical Study Report (see Section 12.1.10.2). A summary of the clinical study report (according to ICH E3 / CPMP/ICH137/95 (35)) should be sent to the Regulatory Authorities and IEC according to the relevant guidelines. For the preparation of a manuscript with the clinical study data for publication in a scientific journal, Dr. Dagmar Wilsmann-Theis and Professor Dr. Rotraut Mössner from the Department of Dermatology at the UMG (*Universitätsmedizin Göttingen*) in Göttingen will be responsible after discussion with the sponsor.

Neither information nor unpublished data given to the investigator may be transmitted to the third party without written approval of the sponsor. The investigator agrees that it is not his duty to either register or to disclose the study results in the context of the global industry position.

Neither information nor unpublished data from exploratory analyses given to the investigator or sponsor may be transmitted to a third party without written approval of the person responsible for the exploratory analyses. For the preparation of a manuscript with the data from the exploratory analyses for publication in a scientific journal, Dr. Robert Sabat will be responsible after discussion with the sponsor, Dr. Dagmar Wilsmann-Theis and Professor Dr. Rotraut Mössner.

The investigator shall be permitted to use the scientific findings gained upon completion of the whole study, meaning after the final report has been transferred to the regulatory database (i) for their own scientific, non-commercial teachings and (ii) to publish these for non-commercial purposes in accordance with the following stipulations:

(a) Any publication of data and findings prior to publication of the whole study results by the sponsor is not permitted. That restriction shall be void, if the sponsor did not publish the whole study results within 18 month after completion of the whole study.

(b) The study data being scientifically published or the use of the study data in another publication by the parties is only allowed after publication of the whole study results by the sponsor or after expiring date set forth above, respectively and shall only be published according to the following process:

  (aa) No less than 60 days prior to a study-related manuscript or other study-related materials are to be filed or submitted with a third individual for publication the investigator shall provide the sponsor with a copy of such manuscript and / or the materials. The sponsor has 60 days from the time of receipt to review these and to comment.

  (bb) In the event the sponsor presents proposals for modification the investigator agrees to consider these in the planned publication unless the proposals for modification compromise the scientific nature or the neutrality of the publication. In the event of a dispute pertaining to the contents of the publication the parties will strive to enclose these in the form of a scientific debate.

  (cc) The investigator further agrees to postpone the publication by an additional 60 days, if and when required in the opinion of the sponsor to protect intellectual property.

(dd) The investigator agrees to maintain confidentiality on the information to be published for the testing time and the extended disqualification period mentioned above.

The sponsor shall not use the investigator's name in any publication without the prior written permission of the investigator. The investigator shall not use the sponsor's name in any publication without the prior written permission of the sponsor.

20 References

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21 Appendices

21.1 Appendix I - Dermatology Life Quality Index (DLQI)

To be filled out by the patient:

The Dermatology Life Quality Index or DLQI, developed in 1994, was the first dermatology-specific Quality of Life instrument. It is a simple 10-question validated questionnaire which has been used in 33 different skin conditions in 33 countries and is available in 85 languages. Its use has been described in over 800 publications including many multinational studies. At present the DLQI is the most frequently used instrument in studies of randomized controlled studies in dermatology. (http://www.dermatology.org.uk/quality/dlqi/quality-dlqi.html, accessed 17-JUN-2011)

The DLQI questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self-explanatory and is handed to the patient who is asked to fill it in without the need for detailed explanation. It addresses the disease-related quality of life over the last 7 days.

The questionnaire contains the following questions:

1. Over the last week, how itchy, sore, painful or stinging has your skin been?
2. Over the last week, how embarrassed or self-conscious have you been because of your skin?
3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?
4. Over the last week, how much has your skin influenced the clothes you wear?
5. Over the last week, how much has your skin affected any social or leisure activities?
6. Over the last week, how much has your skin made it difficult for you to do any sport?
7. Over the last week, has your skin prevented you from working or studying?

   If ‘No’, over the last week how much has your skin been a problem at work or studying?
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?
9. Over the last week, how much has your skin caused any sexual difficulties?
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?

Scoring

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question unanswered	scored 0
Question 7: ‘prevented work or studying’	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

Meaning of DLQI Scores

0 to 1	=	no effect at all on patient's life
2 to 5	=	small effect on patient's life
6 to 10	=	moderate effect on patient's life
11 to 20	=	very large effect on patient's life
21 to 30	=	extremely large effect on patient's life

Interpretation of incorrectly completed questionnaires

There is a very high success rate of accurate completion of the DLQI. However, sometimes patients do make mistakes.

- If one question is left unanswered this will be scored 0 and the scores will be summed and expressed as usual out of a maximum of 30.
- If two or more questions are left unanswered the questionnaire will not be scored.
- If question 7 is answered 'yes' this will be scored 3. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this will then be scored 2 or 1.
- If two or more response options are ticked, the response option with the highest score will be recorded.
- If there is a response between two tick boxes, the lower of the two score options will be recorded.

(32)

21.2 Appendix II - Psoriasis Area and Severity Index (PASI)

To be assessed by the investigator:

The Psoriasis Area and Severity Index (PASI) is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that ranges from 0-72.

The severity of the disease is calculated by scoring the signs of the disease (erythema, induration and scaling) for each of the following 4 body-regions: head (h), trunk (t), upper extremities (u) and lower extremities (l). The scoring system for the signs of the disease is: 0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 = No involvement

1 = 1% to 9% involvement

2 = 10% to 29% involvement

3 = 30% to 49% involvement

4 = 50% to 69% involvement

5 = 70% to 89% involvement

6 = 90% to 100% involvement

To help with the area assessment, the following conventions should be noted:

a. The neck is considered part of the head

b. The axillae and groin are part of the trunk

c. The buttocks are part of the lower extremities

The PASI formula is:

$PASI = 0.1(E_h + I_h + S_h) A_h + 0.3 ((E_t + I_t + S_t) A_t + 0.2 (E_u + I_u + S_u) A_u + 0.4 (E_l + I_l + S_l) A_l$

where E = erythema, I = induration , S = Scaling, and A = area.

(33)

21.3 Appendix III: Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI)

To be assesses by the investigator:

The severity of the disease is calculated by scoring the signs of the disease (erythema, pustules and scaling) for each of the following 4 body-regions: right palm (RP), left palm (LP), Right Sole (RS) and Left Sole (LS). The scoring system for the signs of the disease is: 0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 = No involvement

1 = 1% to 9% involvement

2 = 10% to 29% involvement

3 = 30% to 49% involvement

4 = 50% to 69% involvement

5 = 70% to 89% involvement

6 = 90% to 100% involvement

Body region	**Erythema (E)**	**Pustules / (P) vesicles**	**Scaling (D) (desquamation)**	**Area score (A) (based on true Area %) ***
Right palm (RP)	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = no Involvement 1 = >0 - < 10% 2 = 10 - <30% 3 = 30 - <50% 4 = 50 - <70% 5 = 70 - <90% 6 = 90 - 100%
Left palm (LP)	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = no Involvement 1 = >0 - < 10% 2 = 10 - <30% 3 = 30 - <50% 4 = 50 - <70% 5 = 70 - <90% 6 = 90 - 100%
Right sole (RS)	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = no Involvement 1 = >0 - < 10% 2 = 10 - <30% 3 = 30 - <50% 4 = 50 - <70% 5 = 70 - <90% 6 = 90 - 100%
Left sole (LS)	0 = none 1 = slight	0 = none 1 = slight	0 = none 1 = slight	0 = no Involvement

	2 = moderate 3 = severe 4 = very severe	2 = moderate 3 = severe 4 = very severe	2 = moderate 3 = severe 4 = very severe	1 = >0 - < 10% 2 = 10 - <30% 3 = 30 - <50% 4 = 50 - <70% 5 = 70 - <90% 6 = 90 - 100%

The PPPASI score is calculated using the formula:

PPPASI = 0.2 (ERP + PRP + DRP) ARP + 0.2 (ELP + PLP + DLP) ALP + 0.3 (ERS + PRS + DRS) ARS + 0.3 (ELS + PLS + DLS) ALS

(36)

21.4 Appendix IV - Physician's Global Assessment (PGA)

To be assessed by the investigator:

Assessment of the average severity of all skin lesions at the assessment timepoint according to the following categories:

Score	Category	Description
0	Clear	**Plaque elevation** = 0 (no elevation over normal skin) **Scaling** = 0 (no evidence of scaling) **Erythema** = 0 (except for residual hyperpigmentation/ hypopigmentation)
1	Almost Clear	**Plaque elevation** = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) **Scaling** = ± (surface dryness with some desquamation) **Erythema** = ± (faint, diffuse pink or slight red coloration)
2	Mild	**Plaque elevation** = slight (slight but definite elevation, typically edges are indistinct or sloped) **Scaling** = fine (fine scale partially or mostly covering lesions) **Erythema** = mild (light red coloration)
3	Moderate	**Plaque elevation** = marked (marked definite elevation with rough or sloped edges) **Scaling** = coarser (coarser scale covering most or all of the lesions) **Erythema** = moderate (definite red coloration)
4	Severe	**Plaque elevation** = marked (marked elevation typically with hard or sharp edges) **Scaling** = coarser (coarse, non tenacious scale predominates covering most or all of the lesions) **Erythema** = severe (very bright red coloration)

Adapted from (37)

21.5 Appendix V - Dynamic Hand and Feet (H&F) PGA

To be assesses by the investigator:

Assessment of the global improvement of the H&F Psoriasis lesions compared from baseline to the assessment timepoint, reflecting a global consideration of at least erythema, scaling, plaque thickness, fissuring and postulation according to the following categories:

Category	**Percentage Improvement**	**Category Description**
Cleared (0)	100%	Remission of all clinical signs and symptoms as compared with baseline, except for residual manifestations such as mild erythema
Excellent (1)	75% - 99%	Improvement of all clinical signs and symptoms as compared with baseline, except for residual manifestations such as mild erythema
Good (2)	50% - 74%	Improvement of all clinical signs and symptoms as compared with baseline
Fair (3)	25% - 49%	Improvement of all clinical signs and symptoms as compared with baseline
Slight (4)	1% - 24%	Improvement of all clinical signs and symptoms as compared with baseline
Unchanged (5)		Clinical signs and symptoms unchanged from baseline
Worse (6)		Clinical signs and symptoms deteriorated from baseline

(38)

21.6 Appendix VI - Hand and Feet (H&F) PGA

To be assessed by the investigator:

Assessment of the average severity of the H&F Psoriasis skin lesions at the assessment timepoint according to the following categories:

Score	Category	Category Description
0	Clear	No signs of plaque psoriasis on the hands and / or feet
1	Almost Clear	Just perceptible erythema and just perceptible scaling on the hands and/ or feet
2	Mild	Light pink erythema with minimal scaling and with or without pustules on the hands and / or feet
3	Moderate	Dull red, cleary distinguishable erythema with diffuse scaling, some thickening of the skin, with or without fissures, and with or without pustule formation on the hands and / or feet
4	Severe	Deep/ dark red erythema with cleary obvious and diffuse scaling and thickening, and numerous fissures with or without pustule formation on the hands and / or feet

(28)

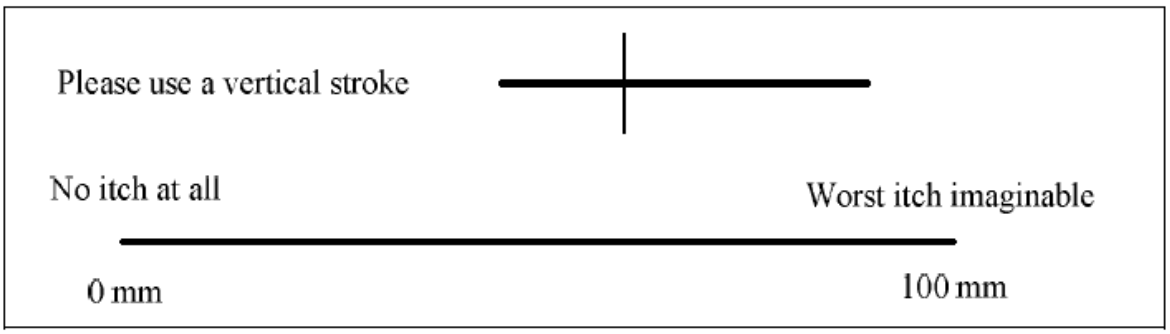
21.7 Appendix VII - Visual Analogue Scale (VAS)

To be filled out by the patient:

Scale will be exactly 100mm in length with a statement at each end representing one extreme of the dimension being measured (e.g. intensity of itch, discomfort or pain). After short explanation by the treating physician, patient will put a vertical bar at that point of the scale which reflects the current patients' subjective status best.

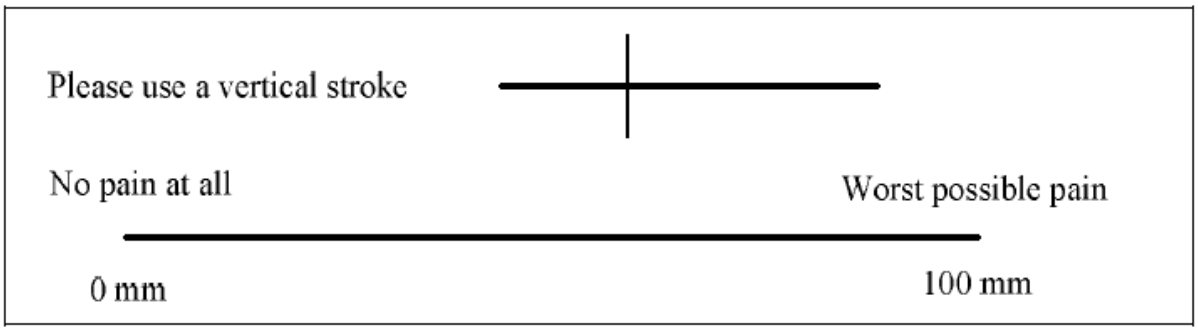
Patient's assessment of pruritus / itch

On average, how much itch have you had because of your condition in the past week?



Patient's assessment of skin discomfort / pain

On average, how much skin discomfort / pain have you had because of your condition in the past week?



Please note: VAS above is not drawn to scale and is for illustrative purpose only.

(39)