CLINICAL STUDY PROTOCOL

Title:	A Phase 3, Randomized, Double-Blind, Placebo- and Active-Controlled Study of the Efficacy and Safety of Daily Piclidenoson (CF101) Administered Orally in Patients with Moderate-to-Severe Plaque Psoriasis
Test Drug:	Piclidenoson (CF101)
Protocol Identification:	CF101-301PS
Sponsor:	Can-Fite BioPharma, Ltd. 10 Bareket Street, Petach Tikva, Israel +972 3 924 1114
Compliance Statement:	The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals For Human Use and all applicable national and local regulations.
Date of Protocol:	14 August 2017, Version 1.0
Date of Amendments:	Amendment 1, 22 January 2018 Amendment 2, 28 September 2018 Amendment 3, 8 October 2018 Amendment 4, 25 June 2019 Amendment 5, 6 April 2020 Amendment 6, 14 December 2020

Michael H. Silverman, MD **Medical Monitor**	Signature: Michael H. Silverman — Date: 14 December 2020
Prof. Pnina Fishman, PhD **Chief Executive Officer**	Signature: P. Fishman — Date: 14 December 2020

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1.0 SYNOPSIS

Compound:

Piclidenoson (CF101)

Protocol No. and Title:

CF101-301PS: A Phase 3 Randomized, Double-Blind, Placebo- and Active-Controlled Study of the Efficacy and Safety of Daily Piclidenoson (CF101) Administered Orally in Patients with Moderate-to-Severe Plaque Psoriasis

Study Objectives:

The primary objectives of this study are to:

- Evaluate the efficacy of oral piclidenoson 2 mg or 3 mg twice daily (BID) in patients with moderate-to-severe plaque psoriasis, compared with placebo, as determined by the proportion of subjects who achieve a Psoriasis Area and Severity Index (PASI) score response of ≥75% (PASI 75) at Week 16 (superiority); and
- Evaluate the safety of oral piclidenoson in this patient population.

The secondary objectives of this study are to:

- Evaluate the efficacy of oral piclidenoson 2 mg or 3 mg BID, compared with placebo, as determined by the proportion of subjects who achieve, respectively, PASI 50, Physician Global Assessment (PGA) score of 0 or 1, and improvement on the Psoriasis Disability Index (PDI) at Week 16 (superiority);
- Evaluate the efficacy of oral piclidenoson 2 mg or 3 mg BID, compared with apremilast, as determined by the proportion of subjects who achieve PASI 75, PGA score of 0 or 1, PASI 50 (non-inferiority), and improvement in PDI at Weeks 16 and 32;
- Establish assay sensitivity within this trial by comparing the efficacy of apremilast 30 mg BID with that of placebo tablets BID, as determined by the proportion of subjects who achieve PASI 75, PGA score of 0 or 1, PASI 50, and improvement in PDI at Week 16 (superiority);
- Determine pharmacokinetics (PK) of piclidenoson under the circumstances of this trial using sparse sampling; and
- Evaluate the relationship between pre-treatment whole blood A_3 adenosine receptor (A_3AR) expression levels and response to piclidenoson treatment.

Study Design, Duration of Treatment:

This is a multicenter, randomized, double-blind, placebo- and active-controlled, adaptive study in adult males and females, aged 18 to 80 years, inclusive, with a diagnosis of moderate-to-severe chronic plaque psoriasis.

At the Screening Visit (Visit 1, performed within 4 weeks prior to randomization), patients who provide written informed consent will have screening procedures performed, including a complete medical history, medication history, physical examination (including height, weight, sitting blood pressure, pulse rate and temperature), assessment of psoriasis (including PASI score, PGA, body surface area involved [BSA], and clinical laboratory tests as defined in Appendix 1.

Eligible subjects will be randomly assigned to piclidenoson 2 mg, 3 mg, matching apremilast 30 mg BID, or matching placebo, in a 3:3:3:2 ratio. Blinding will be maintained using a double-dummy technique. The dosing schedule and blinding scheme will also titrate the apremilast dose in accordance with the approved Summary of Product Characteristics (Appendix 6). The first dose of study medication will be given in the clinic and subjects will remain under observation for at least 1 hour following that dose.

Medication will be taken orally BID for 32 weeks in a double-blinded fashion. Subjects initially assigned to the placebo group will be re-randomized at Week 16 to either piclidenoson 2 mg, piclidenoson 3 mg, or apremilast (with appropriate dose titration) in a 1:1:1 ratio and treated through Week 32, while subjects originally assigned to 1 of the active treatment groups will remain on that treatment through Week 32. The primary efficacy endpoint will be assessed at Weeks 16 and 32.

Disease will be assessed using PASI (Appendix 3), static PGA (Appendix 2), the percentage of BSA involved, and PDI. Subjects will return for assessments and a new supply of study medication at Weeks 4, 8, 12, 16, 20, 24, and 28, and for final study assessments at Week 32. PK will be assessed in a subgroup of approximately 120 subjects at Weeks 0, 8, 16, 24 and 32. PK will be assessed through sparse sampling. Assessment of whole blood A_3AR expression levels will occur at Baseline and is required for approximately 100 randomized patients. PK sampling for all subjects was suspended under previous protocol amendment 5.

After approximately 50% of the subjects reached Week 16, enrollment was paused for an interim analysis of the data through Week 16 for the entire population. The objectives of the interim analysis were to test for superiority of CF101 versus placebo, determine whether to increase the sample size, evaluate the potential for dropping one of the CF101 treatment arms, or declare futility. Further details of the interim analyses are provided in a separate Interim Analysis Plan (IAP). An IDMC Charter was prepared to describe the role of the IDMC in reviewing the interim analysis results and communicating recommendations to the Sponsor.

Based on the results of the interim analysis and recommendations of the IDMC, the Sponsor has decided to continue enrollment in this study, as described in Protocol Amendment 6. The study is continuing using the original dosing groups, randomization schedule, and primary endpoint sample size.

Inclusion Criteria:

1. Male or female, 18 to 80 years of age, inclusive;
2. Diagnosis of moderate-to-severe chronic plaque-type psoriasis with BSA involvement ≥10%, as judged by the Investigator;
3. PASI score ≥12 (Appendix 3)
4. Static PGA ≥3 (Appendix 2)
5. Candidate for systemic treatment or phototherapy for psoriasis;
6. Duration of psoriasis of at least 6 months;
7. Females of childbearing potential must have a negative serum pregnancy test at screening;
8. Female subjects of childbearing potential must use highly effective contraception throughout the course of the trial and for 3 months after. Highly effective methods include hormonal contraception (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants; each method must be used with a barrier method, preferably male condom), intrauterine device or system, tubal ligation, partner vasectomy, or dual (male plus female) barrier methods (each barrier method must be used with a hormonal method). Female subjects who use a hormonally based method must agree to use it in conjunction with a barrier method. Female partners of male study subjects should consider using one of the above methods of contraception as well. Post-menopausal status is defined as menopause for at least 1 year prior to the Screening Visit and must be confirmed by an elevated serum FSH level;
9. Male subjects must refrain from sperm donation during treatment and until at least 90 days after the end of study drug dosing. Male subjects with fertile or pregnant partners must agree to use condoms throughout the course of the trial and for 3 months after;
10. Ability to complete the study in compliance with the protocol; and
11. Ability to understand and provide written informed consent.

Exclusion Criteria:

1. Psoriasis limited to erythrodermic, guttate, palmar, plantar, or generalized pustular psoriasis in the absence of plaque psoriasis;
2. Prior treatment with apremilast within 4 weeks prior to the Baseline visit, or contraindication to apremilast;
3. Treatment with systemic retinoids, corticosteroids, tofacitinib, or immunosuppressive agents (e.g., methotrexate, cyclosporine) within 4 weeks of the Baseline visit;
4. Treatment with a biological agent (etanercept, adalimumab, efalizumab, infliximab, ustekinumab, alefacept, secukinumab, or others, including investigational agents) within a period of time equal to 5 times its circulating half-life, or 30 days, whichever is longer, prior to the Baseline visit;

5. Treatment with high potency topical dermatological corticosteroids (Class I-III in US, Class III-IV in Europe), Vitamin D analogs, keratolytics, or coal tar (other than on the scalp, palms, groin, and/or soles) within 2 weeks of the Baseline visit;
6. Ultraviolet or Dead Sea therapy within 4 weeks of the Baseline visit, or anticipated need for either of these therapies during the study period;
7. Treatment with lithium, hydroxychloroquine or chloroquine within 2 weeks of the Baseline visit, or anticipated need for such drugs during the study period, unless dose has been stable for 3 months prior to the Screening visit and will remain stable throughout the trial;
8. Serum creatinine level greater than 1.25 times the laboratory's upper limit of normal at Screening;
9. Liver aminotransferase levels greater than 1.5 times the laboratory's upper limit of normal at Screening;
10. QTcF interval on Screening Visit ECG or on average of triplicate Baseline Visit ECGs > 450 milliseconds (msec) for males or > 470 msec for females (except when QT prolongation is associated with right or left bundle branch block, in which case enrollment is allowed);
11. A condition which increases proarrhythmic risk, including hypokalemia, hypomagnesemia, or congenital Long QT Syndrome;
12. Heart disease which is, in the Investigator's judgment, clinically unstable;
13. Ongoing or planned use of a concomitant medication that is on the CredibleMedsTM list of drugs known to cause Torsades des Pointes (Appendix 7);
14. Active gastrointestinal disease which could interfere with the absorption of oral medication;
15. Pregnancy, planned pregnancy, lactation, or inadequate contraception as judged by the Investigator;
16. Active drug or alcohol dependence;
17. History of depression or suicidal ideation within the past year;
18. Concomitant use of strong cytochrome P450 inducers, e.g., rifampin, phenobarbital, phenytoin, carbamazepine;
19. Previous participation in a piclidenoson (CF101) clinical trial, defined as having received at least one dose of study medication;
20. Significant acute or chronic medical or psychiatric illness that, in the judgment of the Investigator, could compromise subject safety, limit the subject's ability to complete the study, and/or compromise the objectives of the study;
21. Participation in another investigational drug or vaccine trial concurrently or within 30 days prior to the Screening visit.

Number of Subjects:

Approximately 407 subjects were initially planned for enrollment in this trial, with 111 subjects per active treatment group and 74 subjects initially assigned to the placebo group. After the interim analysis, the total enrollment number was adjusted to 525 subjects, to achieve the original intended number of 407 subjects to be evaluable for the primary endpoint analysis.

Test Drug:

Piclidenoson (methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-β-D-ribofuronamide) 2 mg or 3 mg tablet, administered BID

Control Drug:

Active: Apremilast (Otezla®), dose-titrated over 6 days to 30 mg BID
Placebo: Matching placebo tablets BID

Study Duration:

A Screening Period of up to 4 weeks will precede a treatment period of up to 32 weeks (11 visits [1 via telephone], up to 36 weeks total for the comparative efficacy trial period).

Study Endpoints:

The efficacy endpoints to be analyzed are:

- Proportion of subjects achieving PASI 75 and PASI 50
- Proportion of subjects achieving PGA of 0 or 1
- Change From Baseline (CFB) in PDI
- CFB and Percent Change From Baseline (PCFB) in PASI Score
- CFB in PGA
- CFB in percentage of BSA involved.

These endpoints will be calculated for all on-therapy visits. The primary efficacy endpoint is the proportion of subjects achieving PASI 75 at Week 16. The secondary efficacy endpoints are the proportion of subjects achieving PGA 0 or 1 at Weeks 16 and 32, PASI 75 at Week 32, PASI 50 at Weeks 16 and 32, and PDI CFB at Weeks 16 and 32. All comparisons to placebo will be superiority analyses. All comparisons between piclidenoson and apremilast using binary response variables will be non-inferiority analyses with a margin of 10% and comparison with respect to continuous variables will be performed as superiority analyses.

Optional body surface photographs may be obtained for the clinical record at Baseline, Week 16, and Week 32, but will not be subjected to formal analysis.

Safety endpoints include treatment-emergent adverse events (TEAEs) and changes in vital signs, physical examination, clinical laboratory tests (liver, kidney, hematology, chemistry and urinalysis), and ECG findings.

PK will be assessed through sparse sampling through Week 32.

Sample Size Estimation:

Approximately 407 subjects were initially planned for enrollment in this trial, with 111 subjects per active treatment group and 74 subjects initially assigned to the placebo group. After the interim analysis, the total enrollment number was adjusted to 525 subjects, to achieve the original intended number of 407 subjects to be evaluable for the primary endpoint analysis.

A sample size of 111 subjects for each dose of piclidenoson and 74 subjects for placebo will provide global power of at least 80% for a 0.05 level (2-sided) test using Hochberg's step-wise procedure with the normal approximation for comparing 2 binomial proportions if the probability of achieving PASI 75 is 25% for the less effective dose of piclidenoson and 10% for placebo.

Assuming the probability of achieving PASI 75 at Week 32 is 35% for the less effective dose of piclidenoson and 28% for apremilast, a sample size of 111 subjects per active treatment group will provide power of at least 69% for exhibiting the non-inferiority of at least one dose of piclidenoson to apremilast at Week 32 using a level 0.025 (2-sided) test with the normal approximation for comparing 2 binomial proportions. Conditional power will be computed as part of the interim analysis to determine whether an increase in sample size is required to meet protocol efficacy objectives.

Statistical Analysis:

The significance level for the final analysis will be adjusted to account for the conduct of a single interim analysis. As such, all hypothesis tests for the final study analysis for comparison of piclidenoson to placebo and apremilast will be performed at an overall level of 0.048 using Hochberg's procedure to control the significance level for multiple comparisons. Inference for non-inferiority will be performed using the hypothesis testing formulation for the normal approximation to the binomial, with a non-inferiority margin of 10% and an overall level of 0.048.

All subjects who have received at least 1 dose of study medication will be included in the Safety Population. All analyses of safety will be performed for the Safety Population. Efficacy analyses will be presented for the intent-to-treat (ITT) population, which will consist of all subjects in the Safety Population with PASI recorded for at least 1 post-Baseline visit, and for the Per Protocol population, which will consist of all subjects in the ITT population who had no major protocol violations on or before the Week 32 visit and who complete Week 16 of the study, where the duration between Baseline and Week 16 is at least 15 weeks (105 days). Analyses will be performed using both the ITT and Per Protocol populations. For comparison of piclidenoson to

placebo and comparison of apremilast to placebo, the ITT population will be primary, and the analyses for the Per Protocol population will be secondary. For comparison of piclidenoson to apremilast, the analyses for the Per Protocol population will be primary, and the analyses for the ITT population will be secondary.

The primary analysis is the comparison of both doses of piclidenoson to placebo to establish superiority of either dose of piclidenoson with respect to the proportions of subjects achieving PASI 75 at Week 16. The secondary analyses will be comparison of both doses of piclidenoson to apremilast to establish non-inferiority with respect to the proportions of subjects achieving PASI 75 at Weeks 16 and 32.

Secondary analyses for the comparison of both doses of piclidenoson to placebo to establish superiority of either dose of piclidenoson will be comparison with respect to the proportions of subjects achieving PASI 50, the proportions of subjects achieving PGA of 0 or 1; and PDI CFB at Week 16. Ancillary analyses for comparison of piclidenoson to placebo will be comparison with respect to these variables at all visits prior to Week 16 and comparison with respect to the CFB and PCFB in PASI Score and CFB in percentage of BSA involved at all visits through Week 16.

Analyses of the proportion of subjects achieving PASI 75, PASI 50, and PGA of 0 or 1 at each visit through Week 16 will be performed separately for subjects with PASI Score ≤ 25 at Baseline and those with PASI Score >25 at Baseline.

The comparison of both doses of piclidenoson to apremilast will be performed with respect to the proportion of subjects achieving PASI 50 and PGA of 0 or 1 (non-inferiority), and PDI CFB at Weeks 16 and 32. Ancillary analyses for comparison of piclidenoson to apremilast will be comparison with respect to these variables at all other visits. The comparison of apremilast to placebo with respect to the proportions of subjects achieving PASI 75, PASI 50, and PGA score of 0 or 1 at Week 16 will be performed to establish assay sensitivity.

Subjects with missing values due to discontinuation for binary variables will be considered treatment failures post-discontinuation, referred to as Non-Responder Imputation; intermediate missing values will be imputed using Last Observation Carried Forward. Analyses of the proportion of subjects achieving PASI 75 and PASI 50 at each visit will also be performed using observed data, i.e., without data imputation, as ancillary analyses. Missing values for continuous variables due to discontinuation will be imputed using Last Observation Carried Forward. Sensitivity analyses will be performed to assess the impact of imputation.

Between-treatment comparisons of each dose of piclidenoson and apremilast to placebo with respect to the proportion of subjects achieving PASI 75, PASI 50, and PGA of 0 or 1 at each post-baseline visit through Week 16 will be performed using the normal approximation to the binomial distribution. Similar analyses will be performed for comparison at visits after Week 16 to placebo at Week 16.

Between-treatment comparisons of each dose of piclidenoson and apremilast to placebo with respect to PDI CFB, CFB and PCFB in PASI Score, and CFB in percentage of BSA involved will be performed for each post-baseline visit through Week 16 using analysis of covariance, with treatment and the corresponding value at Baseline in the model for the ITT Population.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.0 or later). All TEAEs will be summarized by treatment group. Counts and percents will be presented by treatment group for each observed System Organ Class and preferred term as defined in MedDRA.

The preferred terms and System Organ Classes will be summarized in the following set of tables:

- All AEs
- All AEs by maximum level of intensity
- All AEs by closest relationship to the study medication

Safety analyses will also examine laboratory parameters, vital signs, ECG parameters, and physical examination findings.

Population PK analyses will be performed under a separate PK Analysis Plan. PK analysis will include population PK based on sparse sampling and the estimation of maximum concentration, minimum concentration, and area under the curve 0-12 hours at Weeks 0, 8 and 16; and trough and peak plasma levels at Weeks 24 and 32. Dose proportionality, effects of gender, age, and body weight on the PK parameters will be assessed if data permit.

In addition to describing population PK, relationships between body weight and/or body mass index, piclidenoson exposure and efficacy will be explored.

Whole blood A_3AR expression data will be summarized.

2.0 SCHEDULE OF PROCEDURES

Table 2-1: Schedule of Study Procedures

Study Procedure	Screening (≤4 weeks prior to Visit 2)	Baseline Week 0	Week 2	Week 4	Weeks 8, 12, 16, 20, 24, 28	Final Week 32 or Early termination visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visits 5-10	Visit 11 or ET visit[1]
Informed consent	X					
Medical and medication history	X					
Physical examination[2]	X	X				X
Verify inclusion/exclusion criteria	X	X				
Vital signs, weight	X	X		X	X	X
PGA[3]	X	X		X	X	X
BSA involved	X	X		X	X	X
PASI[4]	X	X		X	X	X
PDI		X		X	X	X
Body surface photography[5]		X			X (Week 16 only)	X (Week 32 only)
Safety laboratory tests[6]	X	X		X	X (Weeks 8, 16, 24 only)	X
Serum pregnancy test[7]	X					
Urine pregnancy test[8]		X		X	X	X
12-lead resting ECG[9]	X	X		X	X (Weeks 8, 16, 24 only)	X
PK sampling (not required in current amendment)[10]		X			X	X
Whole blood A_3AR expression[11]		X				
Treatment assignment		X				
Dispense study medication		X[12]		X	X[13]	X
Returned pill count				X	X	X

Study Procedure	Screening (≤4 weeks prior to Visit 2)	Baseline Week 0	Week 2	Week 4	Weeks 8, 12, 16, 20, 24, 28	Final Week 32 or Early termination visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visits 5-10	Visit 11 or ET visit[1]
Telephone call			X			
Adverse event assessments		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X

1. Subjects who discontinue dosing prematurely should have all final examinations performed within 48 to 72 hours of discontinuation.
2. A full physical examination will occur at the Screening visit and at visit 11. A brief physical examination will occur at visit 2. Height is measured at the Screening visit only.
3. See Appendix 2 for a description of PGA.
4. See Appendix 3 for a description of PASI.
5. Baseline and Weeks 16 and 32 only. See Appendix 4 for a description of body surface photography (optional).
6. Safety laboratory tests: complete blood count (CBC) with differential and platelet count, clinical chemistries, renal and liver function tests, serum electrolytes and magnesium, urinalysis. See Appendix 1 for a full description of laboratory tests.
7. A serum pregnancy test will be administered to all females of child-bearing potential. A negative result is required for enrollment in the study.
8. A urine pregnancy test will be administered to all females of child-bearing potential. A negative result is required for continued participation in the study, and results MUST be available prior to dispensing of study drug at each visit.
9. ECG to be performed once at Screening and in triplicate at all other time points; pre-dose at Baseline and all other ECG visits; and 30-60 minutes post-dose at Baseline and all other ECG visits. For all ECGs performed, the following parameters will be collected and reported: PR interval, RR interval, HR, QRS interval, QT interval, QTcF interval, ST segment morphology (normal/abnormal), cardiac rhythm, and overall impression.
10. At Weeks 0, 8 and 16, PK subjects will have samples collected for PK at pre-dose and at 2 of the following post-morning dose time points: 1, 2, 3, 4, 6, and 8 hours. During Weeks 24 and 32, PK subjects will have sample collected for PK at pre-dose and 2-hour post-morning dose. PK sampling will not be performed during the Extension Period. PK sampling for all subjects was suspended under previous protocol amendment 5.
11. Only required for approximately 100 randomized subjects.
12. Dosing with assigned treatment BID on an empty stomach will begin after all Baseline examinations have been completed.
13. Re-randomization of subjects originally randomized to placebo to active drug occurs at the Week 16 visit.

3.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
A_3AR	A_3 adenosine receptor
ACR	American College of Rheumatology
AE	Adverse event
AUC	Area under the curve
BID	Twice daily
BMI	Body Mass Index
BSA	Body surface area
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CFB	Change From Baseline
CFR	Code of Federal Regulations
CRF	Case Report Form
EC	Ethics Committee
ECG	Electrocardiogram
GCP	Good Clinical Practice
IAP	Interim Analysis Plan
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDMC	Interim Data Monitoring Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PASI	Psoriasis Area and Severity Index
PBMC	Peripheral blood mononuclear cell
PCFB	Percent Change From Baseline
PDI	Psoriasis Disability Index
PGA	Physician Global Assessment
PK	Pharmacokinetics
q12h	Every 12 hours
QTcF	QT interval corrected with Fridericia's formula
RA	Rheumatoid arthritis
SAE	Serious adverse event(s)
SD	Standard deviation
TEAE	Treatment-emergent adverse event(s)

Abbreviation	Definition
TNF	Tumor necrosis factor
UV	Ultraviolet

4.0 BACKGROUND INFORMATION

4.1 Background and Literature

Psoriasis is a common dermatologic disease that can cause as much disability as cancer, diabetes, or other major medical illnesses (Miller, 2006). It is a benign, chronic inflammatory skin disorder that probably has a genetic basis (Berger, 2004; Schön, 2005) and is clinically characterized by erythematous, sharply demarcated papules and rounded plaques, covered by silvery micaceous scale. The skin lesions of psoriasis are variably pruritic (McCall, 2005). Estimates of the prevalence of the disease vary due to ethnic factors, but the range is probably from 0.5% to 2% (Schön, 2005).

Psoriasis has several variants, the most common being *plaque psoriasis*. Patients with plaque-type psoriasis will have stable, slowly enlarging silvery white plaques that remain basically unchanged for long periods of time. The most common areas for plaque psoriasis to occur are the elbows, knees, gluteal cleft, and the scalp (Schön, 2005). Involvement tends to be symmetric (McCall, 2005).

Eruptive psoriasis (guttate psoriasis) is most common in children and young adults. It develops acutely as many small erythematous, scaling papules, frequently after an upper respiratory tract infection with β-hemolytic streptococci (Schön, 2005). Grave, occasionally life-threatening forms (generalized pustular and erythrodermic psoriasis) may rarely occur (Miller, 2006).

The etiology of psoriasis is poorly understood, but has been linked to HLA-Cw6 and, to a lesser extent, HLA-DR7. Psoriatic lesions are characterized by infiltration of skin with activated T cells, which appear to have a role in the pathophysiology of the disease. Presumably, cytokines from activated T cells elaborate growth factors that stimulate keratinocyte hyperproliferation. Agents that inhibit T cell activation, clonal expansion, or release of proinflammatory cytokines are often effective for treatment (McCall, 2005; Nestle, 2009; Patel, 2011).

Mild psoriasis can generally be managed with topical therapy. Moderate-to-severe psoriasis has traditionally been treated with systemic therapies such as cyclosporine, methotrexate, retinoids, and phototherapy (ultraviolet [UV] B, psoralen plus UV A). The treatments for moderate-to-severe psoriasis often do not meet patient and physician expectations because of significant side effects (e.g., organ toxicity, skin cancer), lack of durable efficacy, and inconvenient administration schedules (e.g., daily dosing, multiple weekly exposures). The recognition of psoriasis as a T-cell mediated disease has led to the development of biologic agents that more specifically target key steps in the pathologic process (Rich, 2004).

4.2 Investigational Product

Piclidenoson (also referred to as CF101) is a selective A_3 adenosine receptor (A_3AR) agonist, under development for the treatment of psoriasis as well as other inflammatory conditions. Adenosine, a ubiquitous purine nucleoside, is released into the extracellular environment by metabolically active and stressed cells. It acts as an important regulatory molecule through its binding to G-protein-associated cell surface receptors identified as A_1, A_2a, A_2b, and A_3 (Linden, 1994; Poulsen, 1998). A_3AR is a 7 trans-membrane Gi-protein coupled receptor. Piclidenoson is a metabolically stable adenosine receptor agonist that binds to and activates A_3AR. It has a very high affinity to the A_3AR (Ki = 0.47 nM) and a very high selectivity (of >1000 fold) over A1 and A2 receptors and it is orally absorbed in animals and humans. For additional information concerning the pharmacology of piclidenoson, please refer to the Investigational Brochure.

4.3 Nonclinical Data

Nonclinical evidence has accumulated suggesting that adenosine-mediated cellular events may have therapeutic relevance in psoriasis and other inflammatory diseases in two separate but related areas. First, it appears that activation of adenosine receptors may play a role in the suppression of tissue damage and inflammatory reactions (Ohta, 2001; Baharav, 2002) and at least part of this effect may be attributable to the inhibition of tumor necrosis factor (TNF)-α production by A_3 receptor activation (Sajjadi, 1996; Salvatore, 2000) and/or the suppression of macrophage inflammatory protein-1α (Szabo, 1998). Piclidenoson or CF101 (termed "IB-MECA" in previous publications) has been shown to exhibit anti-inflammatory activity in at least two such models (Salvatore, 2000; Szabo, 1998; Baharav, 2005). Second, a growing body of preclinical literature suggests that methotrexate exerts much, if not the majority, of its therapeutic effect through an adenosine-dependent mechanism (Montesinos, 2000; Montesinos, 2003).

Piclidenoson has been found to exert a marked anti-rheumatic effect in three different experimental animal models of poly-articular inflammatory arthritis (Baharav, 2005). The anti-inflammatory effect of piclidenoson was examined in rat adjuvant arthritis, in mouse collagen induced arthritis, and in rat tropomyosin induced arthritis. The animals were treated orally once daily with piclidenoson, and the effect on arthritis severity was assessed clinically and histologically in all models. Additionally, the effect of piclidenoson on TNF-α secretion from the synovial tissue, draining lymph nodes, and spleen-derived cells was determined in mice. Piclidenoson at 10 or 100 μg/kg/day markedly ameliorated the clinical and histological features of arthritis in the various autoimmune models. Piclidenoson also inhibited TNF-α secretion in cells derived from mouse synovial tissue, lymph nodes, and spleen.

Piclidenoson acts differentially on pathological and normal cells, due to the fact that the A_3AR target is over-expressed in inflammatory cells. Piclidenoson induces apoptosis of inflammatory cells, while normal cells are refractory to the drug. Furthermore, in distinction from TNF-α blockers, piclidenoson induces only partial inhibition of TNF-α. Thus piclidenoson is not considered to be an immunosuppressive agent and is not expected to present the infection-related risks of therapy with anti-TNF biological agents (Rath-Wolfson, 2006; Bar-Yehuda, 2007; Ohana, 2001; Fishman, 2001; Ochaion, 2009).

4.4 Clinical Data

The safety and pharmacokinetics (PK) behavior of piclidenoson has been evaluated in two separate Phase 1 clinical trials in normal volunteers (for full details of these and other non-psoriasis clinical trials, refer to the Investigational Brochure). In the first study, single oral doses of piclidenoson up to 5 mg were generally safe and well tolerated. At the 10 mg dose, piclidenoson was associated with adverse events (AEs) (headache, nausea, vomiting, flushing) in 3 of the 4 patients. Asymptomatic sinus tachycardia, and mild elevations of systolic blood pressure were also recorded in the 10 mg dose group; these events are presumed to arise from activation of the A_2a receptor, which is thought to exert an effect on the cardiovascular system. In a subsequent trial of twice-daily (BID) repeat-dose testing of piclidenoson, regimens up to 4 mg every 12 hours (q12h) were found to be well-tolerated, with an AE profile comparable to placebo. A dose level of 5 mg q12h was associated with an increased frequency of generally mild and transitory AEs, and occurrences of mild, asymptomatic heart rate increases. Accordingly, a dose of 4 mg twice daily was judged to be the maximum tolerated q12h dose in normal volunteers.

PK analyses showed that piclidenoson was absorbed with dose-proportional increases in maximum concentration (C_{max}) and area under the curve (AUC). After doses of 4 mg q12h for 7 days, mean (standard deviation [SD]) C_{max} was measured at 58.14 (10.4) ng/mL, median (range) time to maximum concentration was 1 (1-2) h, mean (SD) $AUC_{(0\text{-}12\ h)}$ was 458.3 (54.8) ng*h/mL, and mean (SD) half-life was 8.93 (0.8) h. The mean (SD) C_{max} accumulation index, measured as C_{max} (Day 7)/C_{max} (Day 1), was 1.29 (0.24).

An ex vivo analysis of peripheral blood mononuclear cell (PBMC) from patients with active psoriasis has been performed (Ochaion, 2009). In PBMC from psoriasis patients, A_3AR protein was highly over-expressed in comparison to the PBMC of healthy subjects. An increase of A_3AR expression of approximately 16-fold was found in the psoriasis patients over normal control samples, which represents the highest level of A_3AR over-expression documented to date in any population with immune-mediated inflammatory disease. Furthermore, analysis of mRNA in a biopsy of psoriatic skin revealed up-regulation of A_3AR mRNA expression relative to normal skin,

suggesting that piclidenoson, a highly selective A_3AR agonist, may demonstrate a very favorable therapeutic index in this disease. Finally, A_3AR agonism by piclidenoson has been shown to de-regulate the PI3K-NF-kappaB signaling pathway (Fishman, 2006), a pathway which is up-regulated in psoriatic epidermis and suppressed in response to clinically effective therapy (Lizzul, 2005).

In a multi-center, randomized, double-blind, parallel-group, placebo-controlled, dose finding study, 62 patients with moderate-to-severe plaque psoriasis were randomized to treatment with either piclidenoson 1 mg, piclidenoson 2 mg, piclidenoson 4 mg, or placebo given orally every 12 hours for 12 weeks (CF101-201PS) (David, 2011). The incidence of AEs was lowest in the placebo group (6.7%); the incidence of AEs was 64.3% in the piclidenoson 1 mg group, 17.6% in the piclidenoson 2 mg group, and 13.3% in the piclidenoson 4 mg group. TEAEs that were at least possibly related to study medication occurred in 8 (57.1%) of piclidenoson 1 mg patients; 3 (17.6%) of piclidenoson 2 mg patients; 1 (6.7%) of piclidenoson 4 mg patients; and 0 (0.0%) of placebo patients. In the piclidenoson 2 mg group, single instances of chest pain, maxillary and frontal sinusitis, otitis externa, and symptoms of influenza were considered at least possibly related to study medication. Two AEs were rated as severe, both at 1 mg piclidenoson (pruritus and rash); all other AEs were of mild or moderate intensity. No clear patterns of AEs for the piclidenoson treatment groups were evident for individual system organ classes. Treatment with piclidenoson at a dose of 2 mg every 12 hours demonstrated clinical benefit as measured by both Psoriasis Activity and Severity Index (PASI) and Physician Global Assessment (PGA) determinations (David, 2011).

A Phase 2/3 randomized, double-blind, placebo-controlled, dose-finding study of the efficacy and safety of daily piclidenoson administered orally in patients with moderate-to-severe plaque psoriasis was conducted in the US, Israel, Bulgaria, and Romania (CF101-202PS) (David, 2016). Eligible patients were randomly assigned to blinded parallel dosing groups of piclidenoson 1 mg, piclidenoson 2 mg, or matching placebo tablets BID in a 1:1:1 ratio for the 12-week controlled treatment period. At the end of 12 weeks of dosing, all patients assigned to piclidenoson continued piclidenoson at their original dose in blinded fashion, while patients originally assigned to placebo were reassigned in a 1:1 ratio to either piclidenoson 1 mg or piclidenoson 2 mg BID in blinded fashion. Disease was assessed using the static PGA, the percentage of body surface area (BSA) involved, and the PASI.

Following a formal interim analysis, the 1 mg BID dose group was dropped for futility, the sample size was expanded to 127/group, and treatment duration was extended to 16 weeks. After Amendment 4, which was motivated by the results of the interim analysis, the primary efficacy

endpoint changed from the proportion of subjects who achieved PGA of 0 or 1 to the proportion of subjects who achieved PASI 75, with the assessment at Week 12 being the primary analysis and the assessment at Week 16 being a secondary analysis.

The primary efficacy objective of this study was not met: there were no statistically significant differences between treatment groups with respect to PASI 75 at Week 12 (P=0.621). However, separate analyses of subjects enrolled prior to Amendment 4 showed that at Week 12, the proportion of subjects who achieved PASI 75 was greater in the piclidenoson 2 mg group as compared with the placebo group, but did not reach statistical significance (18.2% versus 5.4%, respectively, P=0.096). For unknown reasons, this trend was not maintained for subjects enrolled after Amendment 4.

The secondary analysis of PASI 75 at Week 16 used only data from subjects who enrolled after Amendment 4. The difference between treatment groups was not statistically significant (P=0.658). Furthermore, the secondary analyses of the proportion of subjects who achieved PGA of 0 or 1 at Weeks 12 and 16 were not statistically significant (P=0.256 and P=0.229, respectively).

Within-treatment changes during the open-label extension (OLE) were examined. The proportions of subjects who achieved PASI 75 increased from Week 20 through Week 32. The changes were statistically significant at all visits for both groups (at Week 32 approximately 35% (P<0.001). Results for PASI 50 were similar to those observed for PASI 75. Because of these favorable results, unplanned analyses of PASI 90 and PASI 100 were performed. The proportions of subjects achieving PASI 90 and PASI 100 increased across time in both groups. All within-treatment changes during the OLE were statistically significant for PASI 90. A significant change was observed for PASI 100 in piclidenoson group at Week 32, with 10.6% of subjects achieving PASI 100 (P=0.005).

Statistically significant improvement over time was also observed for the proportion of subjects achieving PGA of 0 or 1 at Weeks 24, 28, and 32 for both treatment groups (P<0.01 for each time point).

Both piclidenoson 1 mg and piclidenoson 2 mg were well tolerated and similar to placebo with respect to frequency, type, and severity of TEAEs. During the blinded period, 37 subjects who received piclidenoson 2 mg (25.5%) and 29 subjects who received placebo (19.6%) experienced at least one TEAE. TEAEs occurred infrequently, and tended to be distributed evenly between treatment groups. Infections and infestations (6.9% of piclidenoson 2 mg subjects and 8.8% of Placebo subjects) were the most frequently reported TEAEs. The majority of TEAEs were mild

and not considered to be related to study medication. The safety profile of piclidenoson 2 mg was similar during the OLE, and for piclidenoson 1 mg (David, 2016).

4.5 Risks and Benefits

Piclidenoson has shown a favorable safety profile in preclinical toxicology testing (see Investigational Brochure). Over 1000 patients with active inflammatory diseases have received piclidenoson in Phase 2 trials, at doses from 0.1 to 4 mg BID for at least 12 weeks. Piclidenoson has been well tolerated, with AE rates generally comparable to placebo (see Investigational Brochure for a comprehensive pooled analysis of AE data). Furthermore, the results of Protocols CF101-201PS and CF101-202PS suggest a favorable therapeutic index in patients with psoriasis. No unique safety risks are anticipated in this trial, which utilizes the same doses and dosing regimens as previous trials.

4.6 Rationale for Current Study and Study Design

The results from nonclinical toxicology studies and clinical safety and efficacy studies performed to date support the safety of piclidenoson and provide evidence of efficacy of piclidenoson as potential therapy for mild-moderate plaque psoriasis. Efficacy data from Protocols CF101-201PS and CF101-202PS demonstrated that piclidenoson 2 mg BID has shown evidence of efficacy in plaque psoriasis as compared to placebo. The current trial will test the higher dose level of 3 mg BID with the expectation that the higher drug exposure will improve efficacy results. Since efficacy of piclidenoson 4 mg BID was not the result in CF101-201PS, 3 mg BID represents the highest piclidenoson dose to be tested.

This trial is randomized, double-blinded, and placebo- and active-controlled, reflecting the current standard of clinical trials in this disease as well as regulatory guidances that require both positive and negative control groups. Likewise, the efficacy assessment instruments represent standards in the field and allow the results of this trial to be compared to those of other, similarly-designed, trials. The 16-week efficacy endpoint will build on the efficacy results of CF101-201PS and CF101-202PS, and likewise conforms to regulatory expectations. For reasons of ethics and patient care, no subject will be treated with placebo for more than 16 weeks, and all enrolled subjects will have an opportunity to receive piclidenoson or the positive control agent, apremilast.

4.7 Population to Be Studied

Eligible subjects will have moderate-to-severe plaque psoriasis and will not have received apremilast, systemic retinoids, corticosteroids, or immunosuppressive agents (e.g., methotrexate, cyclosporine) within 4 weeks prior to initiation of study treatment; biological agents (etanercept, adalimumab, efalizumab, infliximab, ustekinumab, alefacept, secukinumab, or others, including

investigational agents) within a period of time equal to 5 times its circulating half-life, or 30 days, whichever is longer, prior to the Baseline visit; high potency topical dermatological corticosteroids (Class I-III), Vitamin D analogs, keratolytics, or coal tar (other than on the scalp, palms, groin, and/or soles) within 2 weeks prior to initiation of study treatment; or UV or Dead Sea therapy within 4 weeks prior to initiation of study treatment.

5.0 STUDY OBJECTIVES

The primary objectives of this study are to:

- Evaluate the efficacy of oral piclidenoson 2 mg or 3 mg BID in patients with moderate-to-severe plaque psoriasis, compared with placebo, as determined by the proportion of subjects who achieve a PASI score response of >75% (PASI 75) at Week 16 (superiority); and
- Evaluate the safety of oral piclidenoson in this patient population.

The secondary objectives of this study are to:

- Evaluate the efficacy of oral piclidenoson 2 mg or 3 mg BID, compared with placebo, as determined by the proportion of subjects who achieve, respectively, PASI 50, PGA score of 0 or 1, and improvement on the Psoriasis Disability Index (PDI) at Week 16 (superiority);
- Evaluate the efficacy of oral piclidenoson 2 mg or 3 mg BID, compared with apremilast, as determined by the proportion of subjects who achieve PASI 75, PGA score of 0 or 1, and PASI 50 (non-inferiority) and improvement in PDI at Weeks 16 and 32;
- Establish assay sensitivity within this trial by comparing the efficacy of apremilast 30 mg BID with that of placebo tablets BID, as determined by the proportion of subjects who achieve PASI 75, PGA score of 0 or 1, PASI 50, and improvement in PDI at Week 16 (superiority);
- Determine PK of piclidenoson under the circumstances of this trial using sparse sampling; and
- Evaluate the relationship between pre-treatment whole blood A_3AR expression levels and response to piclidenoson treatment.

6.0 STUDY DESIGN

This is a multicenter, randomized, double-blind, placebo- and active-controlled, adaptive study in adult males and females, aged 18 to 80 years, inclusive, with a diagnosis of moderate-to-severe chronic plaque psoriasis.

At the Screening Visit (Visit 1, performed within 4 weeks prior to randomization), patients who provide written informed consent will have screening procedures performed, including a complete medical history, medication history, physical examination (including height, weight, sitting blood

pressure, pulse rate and temperature), assessment of psoriasis (including PASI score, PGA, body surface area involved [BSA], and clinical laboratory tests as defined in Appendix 1.

Eligible subjects will be randomly assigned to piclidenoson 2 mg, 3 mg, apremilast 30 mg BID, or matching placebo, in a 3:3:3:2 ratio. Blinding will be maintained using a double-dummy technique. The dosing schedule and blinding scheme will also titrate the apremilast dose in accordance with the approved Summary of Product Characteristics (Appendix 6). The first dose of study medication will be given in the clinic and subjects will remain under observation for at least 1 hour following that dose.

Medication will be taken orally BID for 32 weeks in a double-blinded fashion. Subjects initially assigned to the placebo group will be re-randomized at Week 16 to either piclidenoson 2 mg, piclidenoson 3 mg, or apremilast (with appropriate dose titration) in a 1:1:1 ratio and treated through Week 32, while subjects originally assigned to 1 of the active treatment groups will remain on that treatment through Week 32. The primary efficacy endpoint will be assessed at Weeks 16 and 32.

Disease will be assessed using PASI (Appendix 3), static PGA (Appendix 2), the percentage of BSA involved, and PDI. Subjects will return for assessments and a new supply of study medication at Weeks 4, 8, 12, 16, 20, 24, and 28, and for final study assessments at Week 32. PK will be assessed at Weeks 0, 8, 16, 24 and 32 in a subgroup of approximately 120 subjects at selected sites. PK will be assessed through sparse sampling. Assessment of whole blood A_3AR expression levels will occur at Baseline, and only for approximately 100 randomized patients. PK sampling for all subjects was suspended under previous protocol amendment 5.

After approximately 50% of the subjects reached Week 16, enrollment was paused for an interim analysis of the data through Week 16 for the entire population. The objectives of the interim analysis were to test for superiority of CF101 versus placebo, determine whether to increase the sample size, evaluate the potential for dropping one of the CF101 treatment arms, or declare futility. Further details of the interim analyses are provided in a separate Interim Analysis Plan (IAP). An IDMC Charter was prepared to describe the role of the IDMC in reviewing the interim analysis results and communicating recommendations to the Sponsor.

Based on the results of the interim analysis and recommendations of the IDMC, the Sponsor has decided to continue enrollment in this study, as described in Protocol Amendment 6. The study is continuing using the original dosing groups, randomization schedule, and primary endpoint sample size.

6.1 Study Duration

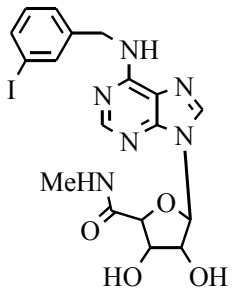
A Screening Period of up to 4 weeks will precede a treatment period of up to 32 weeks (11 visits [1 via telephone], up to 36 weeks total for the comparative efficacy trial period).

6.2 Investigational Drug

6.2.1 Identity of Investigational Product

Piclidenoson, methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-β-D-ribofuronamide (molecular weight 510.29), is a selective A_3AR agonist, the chemical structure of which is shown in Figure 6-1. Piclidenoson is also known as CF101.

Figure 6–1: Piclidenoson (CF101) Chemical Structure



6.2.2 Dispensing and Dosing

Subjects enrolled in each parallel dosing group will receive study medication supplied as tablets.

Study medication will be supplied in blister packs or similar packaging to maintain the blind. Four weeks' supply will be dispensed at each visit. Every 4 weeks the subject will return the used supplies and receive a new 4-week supply, as applicable.

Subjects will also be instructed to take study medication BID on an empty stomach, with water, at least 1 hour before or 2 hours after a meal. Subjects will be instructed to store study medication tablets at room temperature.

6.3 Active Comparator Agent

6.3.1 Identity of Active Comparator Agent

Apremilast will be the active comparator. Refer to the Summary of Product Characteristics in Appendix 6 for details of the prescribing information.

6.3.2 Dispensing and Dosing

Apremilast will be obtained from a commercial source. The dose will be administered orally approximately every 12 hours, and titrated per the Summary of Product Characteristics (Appendix 6), as presented in Table 6-1. No food restrictions are required.

Table 6-1: Apremilast Dose Titration

Day 1		Day 2		Day 3		Day 4		Day 5		Day 6 and Thereafter	
AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	Placebo	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

This schedule will be utilized in Week 1 for subjects randomized to apremilast; and in Week 17 for subjects re-randomized from placebo to apremilast.

Based on apremilast (Otezla) prescribing information, the following precautions should be observed for all subjects in this trial:

- Depression: Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes and if such changes occur to contact their healthcare provider. Carefully weigh risks and benefits of treatment with Otezla in patients with a history of depression and/or suicidal thoughts or behavior.
- Weight Decrease: Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of Otezla.
- Drug Interactions: Use with strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended because loss of efficacy may occur.

6.4 Packaging and Labeling

The study medication will be packaged in blisters and labelled by the Sponsor's clinical supplies designee. Packaging is designed to maintain blinding for piclidenoson, apremilast (including during dose-titration periods), and placebo. Labels will include the statement 'For Investigational Use Only.'

6.5 Investigational Drug Storage and Accountability

The Investigator or designee, which may include the hospital's or institution's Research Pharmacist, will record and acknowledge in writing the receipt of all drug supplies. The study medication will be stored at the temperature listed on the medication's label in the hospital or

institution pharmacy or other locked room accessible only to those individuals authorized by the Investigator to dispense the study medication.

An inventory will be maintained, which will include the description and quantity of medication received. A record will be kept of the medication that is dispensed, to which subject, and the date of dispensing.

At the end of the study, all empty returned and unused drug supplies will be returned to the Sponsor or destroyed in accordance with the Sponsor's instructions.

6.6 Randomization and Blinding

Eligible subjects will be randomly assigned to piclidenoson 2 mg, 3 mg, matching apremilast 30 mg BID, or matching placebo, in a 3:3:3:2 ratio. Blinding will be maintained using a double-dummy technique. PK subjects will be those from selected investigational sites. Blinding will be maintained through over-encapsulation and/or use of a double-dummy or similar packaging technique.

Medication will be taken orally BID for 32 weeks in a double-blinded fashion. Subjects initially assigned to the placebo group will be re-randomized at Week 16 to either piclidenoson 2 mg, piclidenoson 3 mg, or apremilast (with appropriate dose titration) in a 1:1:1 ratio and treated through Week 32, while subjects originally assigned to 1 of the active treatment groups will remain on that treatment through Week 32.

The Investigators, study personnel, subjects, Medical Monitor, and Clinical Monitor will remain blinded to treatment assignment throughout the study, unless safety concerns necessitate unblinding.

If unblinding is required in the interest of subject safety, the Investigator will discuss the matter of unblinding with the Sponsor. In a medical emergency, when knowledge of drug identity is necessary to manage the subject's condition, the Investigator may unblind for that subject without prior consultation with the Sponsor. In that event, the Investigator will notify the Sponsor in writing describing the unblinding circumstances as soon as possible after the randomization code has been broken for the subject.

6.7 Efficacy Variables

- PASI (Feldman, 2005): is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0–4 scale), weighted by the area of involvement (Appendix 3).
- PGA (Gottlieb, 2003) (static): measures the physician's impression of the disease at a single time point (graded on a 0-4 scale; Appendix 2).
- PDI is a patient-reported quality of life questionnaire (Appendix 5).
- Percentage of BSA involved: estimated by using the palm of the hand (without fingers) as equaling 1% BSA.

6.8 Optional Body Surface Photograph

Optional body surface photographs may be obtained for the clinical record but will not be subjected to analysis (Appendix 4).

7.0 SELECTION AND DISCONTINUATION OF SUBJECTS

Subjects for the study will be selected during screening based on the inclusion and exclusion criteria and the clinical assessments listed below.

7.1 Inclusion Criteria

Subjects must meet the following inclusion criteria at Screening, with confirmation at Baseline:

1. Male or female, 18 to 80 years of age, inclusive;
2. Diagnosis of moderate-to-severe chronic plaque-type psoriasis with BSA involvement ≥10%, as judged by the Investigator;
3. PASI score ≥12 (Appendix 3);
4. Static PGA ≥3 (Appendix 2);
5. Candidate for systemic treatment or phototherapy for psoriasis;
6. Duration of psoriasis of at least 6 months;
7. Females of childbearing potential must have a negative serum pregnancy test at screening;
8. Female subjects of childbearing potential must use highly effective contraception throughout the course of the trial and for 3 months after. Highly effective methods include hormonal contraception (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants; each method must be used with a barrier method, preferably male condom), intrauterine device or system, tubal ligation, partner vasectomy, or dual (male plus female) barrier methods (each barrier method must be used with a hormonal method). Female subjects who use a hormonally based method must agree to use it in conjunction with a barrier method. Female partners of male study subjects should consider using one of the above methods of contraception as well. Post-menopausal status is defined as menopause for

at least 1 year prior to the Screening Visit and must be confirmed by an elevated serum FSH level.

9. Male subjects must refrain from sperm donation during treatment and until at least 90 days after the end of study drug dosing. Male subjects with fertile or pregnant partners must agree to use condoms throughout the course of the trial and for 3 months after.
10. Ability to complete the study in compliance with the protocol; and
11. Ability to understand and provide written informed consent.

7.2 Exclusion Criteria

Subjects meeting any of the following criteria at Screening and Baseline will be excluded from the study:

1. Psoriasis limited to erythrodermic, guttate, palmar, plantar, or generalized pustular psoriasis in the absence of plaque psoriasis;
2. Prior treatment with apremilast within 4 weeks prior to the Baseline visit, or contraindication to apremilast;
3. Treatment with systemic retinoids, corticosteroids, tofacitinib, or immunosuppressive agents (e.g., methotrexate, cyclosporine) within 4 weeks of the Baseline visit;
4. Treatment with a biological agent (etanercept, adalimumab, efalizumab, infliximab, ustekinumab, alefacept, secukinumab, or others, including investigational agents) within a period of time equal to 5 times its circulating half-life, or 30 days, whichever is longer, prior to the Baseline visit;
5. Treatment with high potency topical dermatological corticosteroids (Class I-III in US, Class III-IV in Europe), Vitamin D analogs, keratolytics, or coal tar (other than on the scalp, palms, groin, and/or soles) within 2 weeks of the Baseline visit;
6. UV or Dead Sea therapy within 4 weeks of the Baseline visit, or anticipated need for either of these therapies during the study period;
7. Treatment with lithium, hydroxychloroquine or chloroquine within 2 weeks of the Baseline visit, or anticipated need for such drugs during the study period, unless dose has been stable for 3 months prior to the Screening visit and will remain stable throughout the trial;
8. Serum creatinine level greater than 1.25 times the laboratory's upper limit of normal at Screening;
9. Liver aminotransferase levels greater than 1.5 times the laboratory's upper limit of normal at Screening;
10. QTcF interval on Screening Visit ECG or on average of triplicate Baseline Visit ECGs > 450 milliseconds (msec) for males or > 470 msec for females (except when QT prolongation is associated with right or left bundle branch block, in which case enrollment is allowed);

11. A condition which increases proarrhythmic risk, including hypokalemia, hypomagnesemia, or congenital Long QT Syndrome;
12. Heart disease which is, in the Investigator's judgment, clinically unstable;
13. Ongoing or planned use of a concomitant medication that is on the CredibleMeds™ list of drugs known to cause *Torsades des Pointes* (Appendix 7);
14. Active gastrointestinal disease which could interfere with the absorption of oral medication;
15. Pregnancy, planned pregnancy, lactation, or inadequate contraception as judged by the Investigator;
16. Active drug or alcohol dependence;
17. History of depression or suicidal ideation within the past year;
18. Concomitant use of strong cytochrome P450 inducers, e.g., rifampin, phenobarbital, phenytoin, carbamazepine;
19. Previous participation in a piclidenoson (CF101) clinical trial, defined as having received at least one dose of study medication;
20. Significant acute or chronic medical or psychiatric illness that, in the judgment of the Investigator, could compromise subject safety, limit the subject's ability to complete the study, and/or compromise the objectives of the study;
21. Participation in another investigational drug or vaccine trial concurrently or within 30 days prior to the Screening visit.

7.3 Discontinuation from Dosing

Subjects will be discontinued from dosing prematurely if/for:

- Any TEAE occurs that is judged by the Investigator to be related to investigational drug and is classified as Grade 3 or 4 in the Vital Signs, Systemic, or Laboratory Abnormalities tables of the *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, September 2007 [FDA, 2007]);
- The occurrence, in an on-treatment ECG, of an absolute QTcF > 500 msec as determined by the mean of triplicate tracings [Note: This criterion does not apply to subjects with bundle branch block or other intraventricular conduction delay];
- The need for a new concomitant medication known to cause *Torsades des Pointes* (unless approved in advance by the Sponsor), per Appendix 7;
- Other unacceptable toxicity develops;
- The subject so requests;
- Lack of efficacy;
- A need arises for a concomitant medication or therapy prohibited by the protocol;

- The Investigator decides that it is in the subject's best interest;
- The subject is noncompliant with the protocol.

If a subject discontinues dosing prematurely, either at his or her request or at the Investigator's discretion, the primary reason for discontinuation will be recorded on the relevant page of the case report form (CRF). All final visit tasks will be completed within 48 to 72 hours of discontinuation for subjects who discontinue dosing. Subjects who discontinue dosing prematurely due to AEs will be monitored until resolution or stabilization of all AEs.

Subjects who discontinue dosing prematurely will be not replaced.

7.4 Concomitant Medications

Use of any strong cytochrome P450 inducers, e.g., rifampin, phenobarbital, phenytoin, carbamazepine, is prohibited.

Any prescription or over-the-counter medication taken within 30 days prior to the Screening Visit and at any time during the study will be recorded in the appropriate section of the CRF. Use of systemic retinoids, immunosuppressive agents (e.g., methotrexate, cyclosporine), or corticosteroids is prohibited during the study period or within 4 weeks of the Baseline visit. Use of high potency topical dermatological corticosteroids (Class I-III), Vitamin D analogs, keratolytics, or coal tar (other than on the face, scalp, palms, groin, and/or soles) is also prohibited during the study period or within 2 weeks of the Baseline visit. The use of less potent topical dermatological corticosteroids is allowed anywhere on the body, as is the use of bland emollients.

UV or Dead Sea therapy is prohibited within 4 weeks of the Baseline visit, and during the study period.

Treatment with a biological agent (etanercept, adalimumab, efalizumab, infliximab, ustekinumab, alefacept or others, including investigational agents) is prohibited within a period of time equal to 5 times its circulating half-life, or 30 days, whichever is longer, prior to the Baseline visit, and during the study period.

Treatment with lithium, hydroxychloroquine, chloroquine is prohibited during the study period or within 2 weeks of the Baseline visit, unless the dose has been stable for 3 months prior to the Screening visit and remains stable throughout the trial.

While a subject is receiving blinded study drug, the addition of any new medication known to cause *Torsades des Pointes* is prohibited, unless approved in writing by the Sponsor. A list of such medications is provided in Appendix 7 and is accessible at https://crediblemeds.org/.

8.0 STUDY PROCEDURES AND ASSESSMENTS

8.1 Visit 1 (Screening Visit)

At a Screening Visit (performed within 4 weeks prior to the Baseline Visit), subjects who provide written informed consent will have the following procedures performed:

- Complete medical history and medication history
- Full physical examination
- Eligibility based on Screening assessments
- Vital signs, including sitting blood pressure, pulse rate, and temperature; weight; height
- Collect concomitant medication information
- PGA (Appendix 2)
- Percentage of BSA involved
- PASI (Appendix 3)
- Resting 12-lead ECG
- Safety laboratory testing (Appendix 1) (complete blood count [CBC] with differential and platelet count, clinical chemistries, renal and liver function tests, serum electrolytes and magnesium, urinalysis; laboratory samples should be collected AFTER all other assessments have been performed
- Serum pregnancy test (females of child bearing potential)

The Baseline Visit will be scheduled for eligible subjects within 4 weeks of Screening (Visit 1).

8.2 Visit 2 (Baseline Visit)

At the Baseline Visit, eligible subjects will have the following procedures performed:

- Confirm eligibility based on Screening assessments
- Physical examination (brief, documenting changes since the last visit)
- Vital signs, including sitting blood pressure, pulse rate and temperature; weight
- Collect AEs and concomitant medication information
- PGA (Appendix 2)
- Percentage of BSA involved
- PASI (Appendix 3)
- PDI (Appendix 5)
- Optional body surface photography (Appendix 4)

- 12-lead resting ECG (pre-dose, in triplicate; see Exclusion Criterion #10)
- Safety laboratory tests (Appendix 1).
- Whole blood A_3AR expression (note: only required for approximately 100 randomized subjects)
- (No longer required in the current Amendment) PK sampling (samples collected for PK at pre-dose and at 2 of the following post-morning dose time points: 1, 2, 3, 4, 6, and 8 hours)
- Urine pregnancy test (females of child-bearing potential). A negative pregnancy test result is required for continued participation in the study, and results MUST be available prior to dispensing of study drug at each visit.
- Treatment assignment

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled into the study and will receive either piclidenoson 2 mg, piclidenoson 3 mg, apremilast, or matching placebo BID. Enrolled subjects will be sent home with a 4-week supply of the assigned study medication, with instructions to take 1 tablet BID on an empty stomach, 1 hour before or 2 hours after meals. An appointment will be scheduled for Visit 4 to occur at Week 4 (4 weeks ± 3 days following the Baseline Visit).

- ECG (30-60 minutes post-dose, in triplicate)

8.3 Treatment Visit 3 (Week 2)

At Week 2, the site will telephone the subject and inquire about clinical status and compliance, AEs, and concomitant medication information will be recorded. All visits will occur at respective week visit +/- 3 days.

8.4 Treatment Visit 4 (Week 4)

Visit 4 will occur at Week 4 (4 weeks ± 3 days following the scheduled date of Visit 2); subsequent visits will occur 4 weeks ± 3 days following the scheduled date of the previous visit.

- Vital signs, including sitting blood pressure, pulse rate and temperature; weight
- Collect AEs and concomitant medication information
- PGA (Appendix 2)
- Percentage of BSA involved
- PASI (Appendix 3)
- PDI (Appendix 5)
- 12-lead resting ECG (pre-dose, in triplicate)
- Safety laboratory tests (Appendix 1).

- Urine pregnancy test (females of child-bearing potential). A negative pregnancy test result is required for continued participation in the study, and results MUST be available prior to dispensing of study drug at each visit.
- Retrieve drug packs and unused study medication tablets
- Dispense study medication
- ECG (30-60 minutes post-dose, in triplicate)

8.5 Treatment Visits 5-10 (Weeks 8, 12, 16, 20, 24, 28)

All visits will occur at respective week visit +/- 3 days. Subjects will return to the clinic for each visit and have the following procedures performed:

- Collect AEs and concomitant medication information
- Vital signs, including sitting blood pressure, pulse rate and temperature; weight
- PGA (Appendix 2)
- Percentage of BSA involved
- PASI (Appendix 3)
- PDI (Appendix 5)
- Optional body surface photography (Week 16 only; Appendix 4)
- 12-lead resting ECG (pre-dose, in triplicate). Not performed Weeks 12, 20 or 28.
- Safety laboratory tests (Appendix 1). Not performed Weeks 12, 20 or 28.
- Urine pregnancy test (females of child bearing potential). A negative pregnancy test result is required for continued participation in the study, and results MUST be available prior to dispensing of study drug at each visit.
- Retrieve drug packs and unused study medication tablets
- Re-randomization of placebo group subjects to active drug occurs at the Week 16 visit
- Dispense study medication
- ECG (30-60 minutes post-dose, in triplicate). Not performed Weeks 12, 20 or 28.
- (No longer required in the current Amendment) At Weeks 8 and 16, PK subjects will have samples collected for PK at pre-dose and at 2 of the following post-morning dose time points: 1, 2, 3, 4, 6, and 8 hours. During Weeks 24 and 32, PK subjects will have sample collected for PK at pre-dose and 2-hour post-morning dose. For the visits at which PK sampling is performed, the time of the piclidenoson dose will be recorded on the case report form. PK sampling will not be performed during the Extension Period (Section 11.1).

8.6 Final Study Assessment (Visit 11, Week 32) or Early Termination Visit

All visits will occur at respective week visit +/- 3 days. Subjects will return to the clinic and will have the following procedures performed:

- Full physical examination
- Vital signs, including sitting blood pressure, pulse rate and temperature; weight
- Collect AE and concomitant medication information
- PGA (Appendix 2)
- Percentage of BSA involved
- PASI (Appendix 3)
- Optional body surface photography (Week 32 only; Appendix 4)
- 12-lead resting ECG (in triplicate)
- Clinical laboratory tests (Appendix 1)
- Urine pregnancy test (females of child bearing potential)
- (No longer required in the current Amendment) PK subjects will have sample collected for PK during Week 32 at pre-dose and 2-hour post-morning dose. (Section 11.1)
- Retrieve drug packs and unused study medication tablets

Following completion of all procedures, subjects will be discharged from the study.

9.0 ASSESSMENT OF EFFICACY

The efficacy endpoints to be analyzed are:

- Proportion of subjects achieving PASI 75 and PASI 50
- Proportion of subjects achieving PGA of 0 or 1
- Change From Baseline (CFB) in PDI
- CFB and PCFB in PASI Score
- CFB in PGA
- CFB in percentage of BSA involved.

These endpoints will be calculated for all on-therapy visits. The primary efficacy endpoint is the proportion of subjects achieving PASI 75 at Week 16. The secondary efficacy endpoints are the proportion of subjects achieving PGA 0 or 1 at Weeks 16 and 32, PASI 75 at Week 32, PASI 50 at Weeks 16 and 32; and PDI CFB at Weeks 16 and 32. All comparisons to placebo will be superiority analyses. All comparisons between piclidenoson and apremilast using binary response variables will be non-inferiority analyses with a margin of 10% and comparison with respect to continuous variables will be performed as superiority analyses.

Optional body surface photographs may be obtained for the clinical record at Baseline, Week 16, and Week 32, but will not be subjected to formal analysis.

10.0 ASSESSMENT OF SAFETY

Safety endpoints include TEAEs and changes in vital signs, physical examination, clinical laboratory tests (liver, kidney, hematology, chemistry and urinalysis), and ECG findings as described in Section 2.0, Schedule of Procedures.

10.1 Adverse Events

10.1.1 Reporting Adverse Experiences

Any AE (clinical sign, symptom, or disease) temporally associated with the use of the investigational study medication, whether or not considered related to the investigational study medication, shall be documented on the CRF. All AEs reported by the subject or observed by the Investigator will be individually listed. The signs and symptoms, date of onset, stop date, action taken, intensity, frequency, relationship to study treatment, whether or not the AE is an SAE, and the outcome will be reported.

10.1.2 Definitions

An AE is any reaction, side effect, or other untoward event (signs, symptoms, or changes in laboratory data) associated with the use of a test article (drug, biologic, or device), whether or not the event is considered related to the test article. Worsening of the underlying disease is not considered an AE. All AEs occurring after the administration of study medication will be recorded. AEs will be ascertained on the basis of volunteered symptoms and clinical observation and assessment at study visits. AE and concomitant medication information will be recorded during study visits on the appropriate CRF page, and every effort will be made to capture information regarding AEs occurring and concomitant medications taken between visits. All AEs considered to be related to study medication and all SAEs will be followed until resolved or until a stable status has been achieved.

10.1.3 Relationship

The relationship between an AE and the study medication will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

- Definitely Related: An AE that: follows a reasonable temporal sequence from administration of the study medication; follows a known response pattern to the study medication; and, when appropriate to the protocol, is confirmed by improvement after stopping the study medication (positive dechallenge) and by reappearance of the reaction after repeat exposure (positive rechallenge); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.
- Probably Related: An AE that: follows a reasonable temporal sequence from administration of the study medication; follows a known response pattern to the study medication; and,

when appropriate to the protocol, is confirmed by improvement after dechallenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.

- Possibly Related: An AE that: follows a reasonable temporal sequence from administration of the study medication and follows a known response pattern to the study medication but could have been produced by the participant's clinical state or by other therapies.
- Not Related: An AE for which sufficient information exists to indicate that the etiology is unrelated to the study medication. Two or more of the following conditions apply:
  - The AE does not follow a reasonable temporal sequence after administration of the study medication.
  - The AE is readily explained by the participant's clinical state or other therapies.
  - Negative dechallenge – the AE does not abate upon dose reduction or cessation of therapy (assuming that it is reasonable to expect abatement of the AE within the observed interval)

10.1.4 Severity

The intensity of an AE will be assessed as follows:

- Mild: does not interfere with routine activities, can perform daily functions
- Moderate: interferes with routine activities, can perform daily functions, but with concerted effort
- Severe: participant is unable to perform routine activities

10.1.5 Outcome

The outcome of an AE will be assessed as follows:

- Resolved
- Unresolved
- Resolved with sequelae
- Death

10.1.6 Serious Adverse Events

An SAE is any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent disability/incapacity, or a
- Congenital anomaly/birth defect

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Identity of Investigational Products

The Investigator will report all SAEs to the Sponsor within 24 hours of awareness. Determination of expectedness and reporting to relevant regulatory authorities will be determined by the Sponsor. The Investigator is responsible for reporting all SAEs to the Ethics Committee (EC) or Institutional Review Board (IRB) as required by the appropriate regulations.

The Sponsor will notify the relevant regulatory authorities in all relevant countries according to Good Clinical Practice (GCP) and International Council on Harmonisation (ICH) regulations. The Investigator will notify the Sponsor through the following contact:

Name:	Michael H Silverman, MD
Address:	BioStrategics Consulting Ltd, Marblehead, MA, USA
Telephone:	+781 631 8596 (work); +781 639 1349 (home)
Fax:	+781 989 3227
E-mail:	msilverman@biostrategics.com

The Sponsor will notify all sites of any SAE reports it receives. It is each Investigator's responsibility to forward to the hospital's EC/IRB all SAE reports from other sites that are transmitted by the Sponsor.

11.0 ASSESSMENT OF PHARMACOKINETICS

PK will be assessed at Weeks 0, 8, 16, 24 and 32 in a subgroup of approximately 120 subjects at selected sites. PK sampling for all subjects was suspended for subsequent subjects under Protocol Amendment 5.

11.1 Sampling Schedule

PK will be assessed through sparse sampling. The PK sampling schedule is shown in Table 11-1. At Weeks 0, 8, and 16, PK subjects will have samples collected for PK at pre-dose and at 2 of the following post-morning dose time points: 1, 2, 3, 4, 6, and 8 hours. During Weeks 24 and 32, PK subjects will have sample collected for PK at pre-dose and 2-hour post-morning dose. PK sampling will not be performed during the Extension Period.

Table 11-1: PK Sampling Schedule for the Designated PK Sampling Day (Visit)

	Pre-dose	Hour(s) Post-dose					
		1	2	3	4	6	8
Weeks 0, 8, 16	X	X	X	X	X	X	X
Weeks 24 and 32	X		X				

Details of preparation and shipping are presented in the Laboratory Manual.

12.0 ASSESSMENT OF WHOLE BLOOD A_3AR

Assessment of whole blood A_3AR expression levels will occur at Baseline. Details of preparation and shipping are presented in the Laboratory Manual. This assessment is only required for approximately 100 randomized subjects, after which, it need not be collected.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plan

A detailed statistical analysis plan will be prepared and finalized prior to locking the final database and breaking the blind. Details of the interim analysis are provided in the IAP.

The significance level for the final analysis will be adjusted to account for the conduct of a single interim analysis. As such, all hypothesis tests for the final analysis for comparison of piclidenoson to placebo and apremilast will be performed at an overall level of 0.048 using Hochberg's procedure to control the significance level for multiple comparisons. Inference for non-inferiority will be performed using the hypothesis testing formulation for the normal approximation to the binomial, with a non-inferiority margin of 10% and an overall level of 0.048.

Between-treatment comparisons of each dose of piclidenoson and apremilast to placebo with respect to the proportion of subjects achieving PASI 75, PASI 50, and PGA of 0 or 1 at each post-baseline visit through Week 16 will be performed using the normal approximation to the binomial distribution. Similar analyses will be performed for comparison at visits after Week 16 to placebo at Week 16.

Between-treatment comparisons of each dose of piclidenoson and apremilast to placebo with respect to PDI CFB, CFB and PCFB in PASI Score, and CFB in percentage of BSA involved will be performed for each post-baseline visit through Week 16 using analysis of covariance, with treatment and the corresponding value at Baseline in the model for the intent-to-treat (ITT) population.

13.2 Study Populations

All subjects who have received at least 1 dose of study medication will be included in the Safety Population. All analyses of safety will be performed for the Safety Population.

Efficacy analyses will be presented for the ITT population, which will consist of all subjects in the Safety Population with PASI recorded for at least 1 post-Baseline visit, and for the Per Protocol population, which will consist of all subjects in the ITT population who had no major protocol violations on or before the Week 32 visit and who complete Week 16 of the study, where the duration between Baseline and Week 16 is at least 15 weeks (105 days). Analyses of the proportion of subjects achieving PASI 75, PASI 50, PGA of 0 or 1, and PDI CFB will be performed using both the ITT and Per Protocol populations. For comparison of piclidenoson to placebo and comparison of apremilast to placebo, the ITT population will be primary, and the analyses for the Per Protocol population will be secondary. For comparison of piclidenoson to apremilast, the analyses for the Per Protocol population will be primary, and the analyses for the ITT population will be secondary.

13.3 Efficacy Analyses

13.3.1 Primary Efficacy

The primary analysis is the comparison of both doses of piclidenoson to placebo to establish superiority of either dose of piclidenoson with respect to the proportions of subjects achieving PASI 75 at Week 16. The secondary analyses will be comparison of both doses of piclidenoson to apremilast to establish non-inferiority with respect to the proportions of subjects achieving PASI 75 at Weeks 16 and 32.

13.3.2 Secondary Efficacy

Secondary analyses for the comparison of both doses of piclidenoson to placebo to establish superiority of either dose of piclidenoson will be comparison with respect to the proportions of subjects achieving PASI 50, the proportions of subjects achieving PGA of 0 or 1; and PDI CFB at Week 16. Ancillary analyses for comparison of piclidenoson to placebo will be comparison with respect to these variables at all visits prior to Week 16 and comparison with respect to the percentage of BSA involved at all visits through Week 16.

Analyses of the proportion of subjects achieving PASI 75, PASI 50, and PGA of 0 or 1 at each visit through Week 16 will be performed separately for subjects with PASI Score ≤ 25 at Baseline and those with PASI Score >25 at Baseline.

The comparison of both doses of piclidenoson to apremilast will be performed with respect to the proportion of subjects achieving PASI 50 and PGA of 0 or 1 (non-inferiority), and PDI CFB at Weeks 16 and 32. Ancillary analyses for comparison of piclidenoson to apremilast will be comparison with respect to these variables at all other visits. The comparison of apremilast to placebo with respect to the proportions of subjects achieving PASI 75, PASI 50, and PGA score of 0 or 1 at Week 16 will be performed to establish assay sensitivity.

13.3.3 Handling of Missing Data

Subjects with missing values due to discontinuation for binary variables will be considered treatment failures post-discontinuation, referred to as Non-Responder Imputation; intermediate missing values will be imputed using Last Observation Carried Forward. Analyses of the proportion of subjects achieving PASI 75 and PASI 50 at each visit will also be performed using observed data, i.e., without data imputation, as ancillary analyses. Missing values for continuous variables due to discontinuation will be imputed using Last Observation Carried Forward. Sensitivity analyses will be performed to assess the impact of imputation.

13.4 Safety Analyses

Demographic parameters, including age, sex, and ethnic origin at the screening visit, will be summarized for the Safety Population, overall and by treatment group. Age will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum and maximum); sex and ethnic origin will be summarized using frequency counts and percentages. Medical history will be summarized for the Safety Population, overall and by treatment group, using counts and percentages.

Duration of treatment and compliance will be summarized by treatment group for the Safety Population. The subject's compliance rate during the study will be calculated as the total number of tablets dispensed minus the total number of tablets returned divided by twice the total duration of treatment. The summaries of duration of treatment and compliance will be presented for 0-16 weeks and 16-32 weeks.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.0 or later). All TEAEs will be summarized by treatment group. Counts and percents will be presented by treatment group for each observed system organ class (SOC) and preferred term as defined in MedDRA.

The preferred terms and SOCs will be summarized in the following set of tables:

- All AEs;
- All AEs by maximum level of intensity;
- All AEs by closest relationship to the study medication.

A subject having more than one TEAE with the same preferred term in a given time period will be counted only once in the incidence calculation for that preferred term for that time period. Similarly, if a subject has more than one TEAE in the same SOC in a given time period, the subject will be counted only once in the total number of subjects with a TEAE for that SOC for that time period.

Subjects who experience SAEs, subjects who died, and subjects who discontinue dosing prematurely due to unacceptable toxicity will be listed. Concomitant medications will be coded using the World Health Organization Drug dictionary and will be summarized by treatment group using counts and percentages.

Vital signs, including sitting blood pressure (systolic and diastolic), pulse rate, temperature, weight, and body mass index (BMI) will be summarized using descriptive statistics by treatment group and visit for both the observed values and CFB. Height will be summarized only for the screening visit.

For continuous ECG parameters, the actual values and changes from baseline will be summarized by treatment group at each visit using descriptive statistics. Categorical ECG parameters [normal, abnormal-not clinically significant, and abnormal-clinically significant for overall impression; normal, abnormal for ST segment and cardiac rhythm], will be summarized by treatment group using counts and percentages.

Physical examination findings will be summarized by treatment group using counts and percentages.

For each continuous laboratory parameter, descriptive statistics will be presented for the observed value and CFB by treatment group and visit. Urinalysis and pregnancy test results will be included in the by-subject data listings of laboratory parameters but not in the summary tables.

13.5 Pharmacokinetic Analyses

Population PK analyses will be performed under a separate PK Analysis Plan. PK analysis will include population PK based on sparse sampling, and the estimation of C_{max}, minimum concentration (C_{min}), $AUC_{(0\text{-}12h)}$ and $AUC_{(0\text{-}24h)}$ at Weeks 0, 8 and 16; and trough and peak plasma levels at Weeks 24 and 32. Dose proportionality, effects of gender, age, and body weight on the PK parameters will be assessed if data permit.

In addition to describing population PK, relationships between body weight and/or BMI, piclidenoson exposure and efficacy will be explored.

13.6 Whole blood A_3AR

Whole blood A_3AR expression data will be summarized.

13.7 Determination of Sample Size

Approximately 407 subjects were initially planned for enrollment in this trial, with 111 subjects per active treatment group and 74 subjects initially assigned to the placebo group. Based on the results of the interim analysis and recommendations of the IDMC, the Sponsor has decided to continue enrollment in this study, as described in Protocol Amendment 6. The study is continuing using the original dosing groups, randomization schedule, and primary endpoint sample size.

A sample size of 111 subjects for each dose of piclidenoson and 74 subjects for placebo will provide global power of at least 80% for a 0.05 level (2-sided) test using Hochberg's step-wise procedure with the normal approximation for comparing 2 binomial proportions if the probability of achieving PASI 75 is 25% for the less effective dose of piclidenoson and 10% for placebo.

Assuming the probability of achieving PASI 75 at Week 32 is 35% for the less effective dose of piclidenoson and 28% for apremilast, a sample size of 111 subjects per active treatment group will provide power of at least 69% for exhibiting the non-inferiority of at least one dose of piclidenoson to apremilast at Week 32 using a level 0.025 (two-sided) test with the normal approximation for comparing 2 binomial proportions.

At the time of the interim analysis, in accordance with the procedures described in Section 13.8 below, 307 subjects had been enrolled and treated and of those, 189 subjects (i.e., 46% of the final sample size) had completed Week 16 for the primary endpoint analysis. The remaining 118 enrolled subjects who had not completed Week 16 at the time of the interim analysis were prematurely withdrawn from the study. To obtain enough evaluable subjects to satisfy the original power calculations for the study, the originally planned 100 new subjects plus an additional 118 subjects will be enrolled, leading to a total sample size of 525 subjects. That is, following the interim analysis, the study will enroll a total of 218 new subjects. Assuming all 218 new subjects reach the Week 16 time point, this will result in a total of 407 subjects with Week 16 data for the final analysis, as initially planned.

13.8 Interim Analysis

The results of the interim analysis and recommendations of the IDMC are to continue enrollment in this study as shown in Protocol Amendment 6.

After approximately 50% of the subjects reached Week 16, enrollment was paused for an interim analysis of the data for the entire population. Further details of the interim analyses are provided in the IAP.

The objectives of the planned interim analysis were:

- Evaluate efficacy of piclidenoson compared to placebo
- Evaluate efficacy of piclidenoson compared to apremilast
- Determine whether sample size re-estimation should be recommended
- Determine whether dropping one of the piclidenoson dose groups should be recommended
- Determine whether stopping for futility should be recommended

An IDMC Charter was prepared to describe the role of the IDMC in reviewing the interim analysis results and communicating recommendations to the Sponsor. Protocol Amendment 6 reflects the results of the interim analysis and recommendation of the IDMC.

14.0 ETHICS

14.1 Ethical Conduct of the Study

The study will be conducted in compliance with applicable ICH rules, E6 GCP, regulations, and guidelines and applicable laws and regulations of the locale and country where the study is conducted. The study will be conducted with the approval of a duly constituted IRB or EC in accordance with the requirement of United States regulation Title 21 Code of Federal Regulations

(CFR) Part 56 - Institutional Review Boards. The nature and risks of the study will be fully explained to each subject and written consent obtained in accordance with the requirements of 21 CFR 50 - Protection of Human Subjects. Subjects will be informed of their rights, including the right to withdraw from the study at any time.

Body surface photographs of psoriatic lesions may be taken in this study, but will be optional. Any photographs taken will be anonymous and will be labeled only with the subject study identification number.

14.2 Subject Information and Consent

A properly executed, written Informed Consent Form (ICF) in compliance with national and local regulations and GCP guidelines will be obtained from each subject prior to entering the study or performing any unusual or non-routine procedure. The Investigator will submit a copy of the ICF to the IRB/EC for review and approval before research subjects are enrolled. The Investigator will provide a copy of the signed ICF to the subject and a copy will be maintained in the subject's medical record.

14.3 Institutional Review Board/Ethics Committee

The Investigator will provide the IRB/EC with all requisite material, including a copy of the protocol and the ICF. The study will not be initiated until the IRB/EC provides written approval of the protocol and the ICF and until approved documents have been obtained by the Investigator and copies received by the Sponsor. Appropriate reports on the progress of this study by the Investigator will be made to the IRB/EC and the Sponsor in accordance with the applicable government regulations and in agreement with policy established by the Sponsor.

14.4 Monitoring Case Report Forms

Can-Fite or their designee will monitor all aspects of the study with respect to current GCP and standard operating procedures for compliance with applicable regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Investigator.

14.5 Study Record Retention

The Investigator must retain essential documents as listed below for 15 years. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- EC or IRB approvals for the study protocol and all amendments

- All source documents and laboratory records
- CRF copies
- Participants' ICF
- Any other pertinent study document

14.6 Data Quality Assurance

All data recorded during the study will be available for audit against source data and for compliance with GCP and specific protocol requirements. Monitoring of the study progress and conduct will be ongoing. The Sponsor or its designee will be responsible for the following:

- Monitoring study conduct to ensure that the rights of subjects are protected;
- Monitoring study conduct to ensure trial compliance with GCP guidelines; and
- Monitoring accuracy, completion and verification from source documents of study data.

14.7 Confidentiality

All information provided to the Investigator by Can-Fite or their designees, including non-clinical data, protocols, CRFs and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be released in confidence to the EC or IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to Can-Fite or their designees or in confidence to the EC or IRB, except if required by law.

15.0 INVESTIGATOR'S STATEMENT

I have read the protocol entitled "CF101-301PS: A Phase 3, Randomized, Double-Blind, Placebo- and Active-Controlled Study of the Efficacy and Safety of Daily Piclidenoson (CF101) Administered Orally in Patients with Moderate-to-Severe Plaque Psoriasis" and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by Can-Fite BioPharma, Ltd. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by Can-Fite, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

Signature of Principal Investigator	Date (day/month/year)
Printed Name of Investigator	Site Number

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30. Szabo C, Scott GS, Virag L, et al. Suppression of macrophage inflammatory protein (MIP)-1α production and collagen-induced arthritis by adenosine receptor agonists. *Brit J Pharmacol*. 1998; 125: 379-387.

APPENDIX 1: SAFETY LABORATORY TESTS

The following laboratory tests will be performed at those clinic visits specified in Section 2.0.

<table>
<tr><th>Liver and Kidney Tests</th><th>Chemistry Tests</th></tr>
<tr><td>Alanine aminotransferase
Aspartate aminotransferase
Creatinine
Total bilirubin</td><td rowspan="3">Albumin
Alkaline phosphatase
Blood glucose
Blood urea nitrogen
Calcium
Magnesium
Globulin
Phosphorus
Total protein
Uric acid
Electrolytes</td></tr>
<tr><th>Hematology Tests</th></tr>
<tr><td>Complete blood count, including red blood cell indices and white blood cell differential
Platelet count</td></tr>
<tr><th>Urinalysis</th><th>Pregnancy Tests</th></tr>
<tr><td>Specific gravity, and pH, urine glucose, bilirubin, ketones, blood, protein, nitrite, leukocyte esterase, microscopic examination (if appropriate)</td><td>Serum pregnancy test (females of child-bearing potential) at Screening, urine pregnancy tests for all subsequent pregnancy tests; pregnancy test results must be negative for a subject to enroll in the study, and to continue in the study; a positive test result will require a subject to be discontinued from the study. Results MUST be available prior to the dispensing of study drug at each visit.</td></tr>
</table>

APPENDIX 2: PHYSICIAN GLOBAL ASSESSMENT

The PGA (Gottlieb, 2003) will be performed at all clinic visits. A static PGA will be used for this study, in which the physician's impression of the disease at a single time point is measured.

The PGA is recorded on a 5-point scale, from 0 to 4, based on a set of morphological descriptors, as shown below.

- PGA of 0 = Clear; no active lesions
- Plaque elevation: No elevation above normal skin
- Erythema: Normal skin color or post-inflammatory color change; no erythema
- Scaling: No scales

PGA of 1 = Minimal; the qualities across all involved areas show minimal disease activity, as indicated by no more than:

- Plaque elevation: Possible elevation, but difficult to ascertain whether there is slight elevation above normal surrounding skin
- Erythema: Faint erythema, up to light red or pink coloration
- Scaling: Surface dryness with some white coloration

PGA of 2 = Mild; the qualities across all involved areas show mild disease activity, as indicated by no more than:

- Plaque elevation: Slight but definite elevation above surrounding normal skin; the edges are typically indistinct or sloped
- Erythema: Dark pink to definite red coloration
- Scaling: Fine scale partially or mostly covering lesions

PGA of 3 = Moderate; the qualities across all involved areas show moderate disease activity, as indicated by no more than:

- Plaque elevation: Moderate elevation with rough or sloped edges
- Erythema: Moderate, definite red coloration
- Scaling: Coarse scales covering most or all of the lesions;

PGA of 4 = Severe; the qualities across all involved areas show severe disease activity, as indicated by:

- Plaque elevation: Marked elevation, typically with hard and/or sharp edges
- Erythema: Very bright, extreme red to dusky, deep red coloration
- Scaling: Coarse to very coarse; coarse nontenacious to very thick tenacious scales predominate or cover most of the lesions

APPENDIX 3: PSORIASIS AREA AND SEVERITY INDEX

The PASI (Feldman, 2005) will be performed at all clinic visits.

		Head	Upper Extremities	Trunk	Lower Extremities
1	Redness				
2	Thickness				
3	Scale				
4	Sum of Rows 1, 2, and 3				
5	Area score				
6	Score of Row 4 x Row 5 x the area multiplier	Row 4 x Row 5 x0.1	Row 4 x Row 5 x0.2	Row 4 x Row 5 x0.3	Row 4 x Row 5 x0.4
7	Sum Row 6 for each column for PASI score				

_Redness, thickness, and scale are measured on a 0–4 scale (none, slight, mild, moderate, severe)

_Area scoring criteria (score: % involvement)

0: 0 (clear)
1: <10%
2: 10–<30%
3: 30–<50%
4: 50–<70%
5: 70–<90%
6: 90–<100%

Steps in generating PASI score

Divide body into 4 areas: head, arms, trunk to groin, and legs to top of buttocks.

Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0 = clear; 1–4 = increasing severity).

Sum scores of erythema, thickness, and scale for each area.

Generate a percentage for skin covered with psoriasis for each area and convert that to a 0–6 scale (0 = 0%; 1 = <10%; 2 = 10–<30%; 3 = 30–<50%; 4 = 50–<70%; 5 = 70–<90%; 6 = 90–100%).

Multiply score of item (c) above times item (d) above for each area and multiply that by 0.1, 0.2, 0.3, and 0.4 for head, arms, trunk, and legs, respectively.

Add these scores to get the PASI score.

APPENDIX 4: OPTIONAL BODY SURFACE PHOTOGRAPHY

Training and equipment will be standardized across sites, and will be detailed in an operations manual prepared by the Sponsor.

- Four quarter-body photographs will be taken:
- Upper body anterior
- Upper body posterior
- Lower body anterior
- Lower body posterior

Body surface photographs should be obtained using the following procedure (described in greater detail in the operations manual):

- The subject will disrobe completely, including all jewelry and wristwatches, except for the modesty garment provided by the site.
- The subject should be centered against a blue backdrop, and stand on a blue stage 35 cm high.
- The subject's hands must be held close to body with palms facing the camera for anterior views, and the back of the hands facing the camera for posterior views.

The camera lens must be 147 cm (58 inches) from the front of the subject.

APPENDIX 5: PSORIASIS DISABILITY INDEX

Thank you for your help in completing this questionnaire. Please tick one box for every question. Every question relates to the LAST FOUR WEEKS ONLY.

All questions relate to the LAST FOUR WEEKS.

DAILY ACTIVITIES:

1. How much has your psoriasis interfered with you carrying out work around the house or garden?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

2. How often have you worn different types or colours of clothes because of your psoriasis?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

3. How much more have you had to change or wash your clothes?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

4. How much of a problem has your psoriasis been at the hairdressers?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

5. How much has your psoriasis resulted in you having to take more baths than usual?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

There are 2 different versions of questions 6, 7 and 8. If you are **at regular work or at school** please answer the first questions **6 - 8**. If you are **not at work or school** please answer the second questions **6 - 8**.

All questions relate to the LAST FOUR WEEKS.

WORK OR SCHOOL (if appropriate)

6. How much has your psoriasis made you lose time off work or school over the last four weeks?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

7. How much has your psoriasis prevented you from doing things at work or school over the last four weeks?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

8. Has your career been affected by your psoriasis? e.g., promotion refused, lost a job, asked to change a job.

Very much ☐
A lot ☐
A little ☐
Not at all ☐

IF NOT AT WORK OR SCHOOL: ALTERNATIVE QUESTIONS

6. How much has your psoriasis stopped you carrying out your normal daily activities over the last four weeks?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

7. How much has your psoriasis altered the way in which you carry out your normal daily activities over the last four weeks?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

8. Has your career been affected by your psoriasis? e.g., promotion refused, lost a job, asked to change a job.

Very much ☐
A lot ☐
A little ☐
Not at all ☐

All questions relate to the <u>LAST FOUR WEEKS.</u>

<u>PERSONAL RELATIONSHIPS:</u>

9. Has your psoriasis resulted in sexual difficulties over the last four weeks?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

10. Has your psoriasis created problems with your partner or any of your close friends or relatives?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

<u>LEISURE:</u>

11. How much has your psoriasis stopped you going out socially or to any special functions?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

12. Is your psoriasis making it difficult for you to do any sport?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

13. Have you been unable to use, criticised or stopped from using communal bathing or changing facilities?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

14. Has your psoriasis resulted in you smoking or drinking alcohol more than you would do normally?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

TREATMENT:

15. To what extent has your psoriasis or treatment made your home messy or untidy?

Very much ☐
A lot ☐
A little ☐
Not at all ☐

Please check that you have answered all the questions.

Thank you for your help.

APPENDIX 6: OTEZLA® SUMMARY OF PRODUCT CHARACTERISTICS

OTEZLA

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Otezla 10 mg film-coated tablets
Otezla 20 mg film-coated tablets
Otezla 30 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of apremilast.
Each film-coated tablet contains 20 mg of apremilast.
Each film-coated tablet contains 30 mg of apremilast.

Excipient(s) with known effect:

Each film-coated tablet contains 57 mg of lactose (as lactose monohydrate).
Each film-coated tablet contains 114 mg of lactose (as lactose monohydrate).
Each film-coated tablet contains 171 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pink, diamond shaped 10 mg film-coated tablet of 8 mm length with “APR” engraved on one side and “10” on the opposite side.
Brown, diamond shaped 20 mg film-coated tablet of 10 mm length with “APR” engraved on one side and “20” on the opposite side.
Beige, diamond shaped 30 mg film-coated tablet of 12 mm length with “APR” engraved on one side and “30” on the opposite side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Psoriatic arthritis
Otezla, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy (see section 5.1).

Psoriasis
Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

4.2 Posology and method of administration

Treatment with Otezla should be initiated by specialists experienced in the diagnosis and treatment of psoriasis or psoriatic arthritis.

Posology
The recommended dose of Otezla is 30 mg twice daily taken orally, morning and evening, approximately 12 hours apart, with no food restrictions. An initial titration schedule is required as shown below in Table 1. No re-titration is required after initial titration.

Table 1: Dose titration schedule

Day 1	Day2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

If patients miss a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose, the missed dose should not be taken and the next dose should be taken at the regular time.

During pivotal trials the greatest improvement was observed within the first 24 weeks of treatment. If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered. The patient's response to treatment should be evaluated on a regular basis. Clinical experience beyond 52 weeks is not available (see section 5.1).

Special populations
Elderly patients
No dose adjustment is required for this patient population (see sections 4.8 and 5.2).

Patients with renal impairment
No dose adjustment is needed in patients with mild and moderate renal impairment. The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockcroft-Gault equation). For initial dose titration in this group, it is recommended that Otezla be titrated using only the AM schedule listed in Table 1 and the PM doses be skipped (see section 5.2).

Patients with hepatic impairment
No dose adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of apremilast in children aged 0 to 17 years have not been established. No data are available.

Method of administration
Otezla is for oral use. The film-coated tablets should be swallowed whole, and can be taken either with or without food.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Otezla should be dose reduced to 30 mg once daily in patients with severe renal impairment (see sections 4.2 and 5.2).

Patients who are underweight at the start of treatment should have their body weight monitored regularly. In the event of unexplained and clinically significant weight loss, these patients should be evaluated by a medical practitioner and discontinuation of treatment should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of strong cytochrome P450 3A4 (CYP3A4) enzyme inducer, rifampicin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. Therefore, the use of strong CYP3A4 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin and St. John's Wort) with apremilast is not recommended. Co-administration of apremilast with multiple doses of rifampicin resulted in a decrease in apremilast area-under-the-concentration time curve (AUC) and maximum serum concentration (C_{max}) by approximately 72% and 43%, respectively. Apremilast exposure is decreased when administered concomitantly with strong inducers of CYP3A4 (e.g. rifampicin) and may result in reduced clinical response.

In clinical studies, apremilast has been administered concomitantly with topical therapy (including corticosteroids, coal tar shampoo and saliycyilic acid scalp preparations) and UVB phototherapy.

There was no clinically meaningful drug-drug interaction between ketoconazole and apremilast. Apremilast can be co-administered with a potent CYP3A4 inhibitor such as ketoconazole.

There was no pharmacokinetic drug-drug interaction between apremilast and methotrexate in psoriatic arthritis patients. Apremilast can be co-administered with methotrexate.

There was no pharmacokinetic drug-drug interaction between apremilast and oral contraceptives containing ethinyl estradiol and norgestimate. Apremilast can be co-administered with oral contraceptives.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Pregnancy should be excluded before treatment can be initiated. Women of childbearing potential should use an effective method of contraception to prevent pregnancy during treatment.

Pregnancy
There are limited data about the use of apremilast in pregnant women.

Apremilast is contraindicated during pregnancy. Effects of apremilast on pregnancy included embryofetal loss in mice and monkeys, and reduced fetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. No such effects were observed when exposure in animals was at 1.3-fold the clinical exposure (see section 5.3).

Breast-feeding
Apremilast was detected in milk of lactating mice (see section 5.3). It is not known whether apremilast, or its metabolites, are excreted in human milk. A risk to the breastfed infant cannot be excluded, therefore apremilast should not be used during breast-feeding.

Fertility
No fertility data is available in humans. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels 3-fold clinical exposure and in females at exposure levels 1-fold clinical exposure. For pre-clinical fertility data see section 5.3.

4.7 Effects on ability to drive and use machines

Apremilast has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions in Phase III clinical studies have been gastrointestinal (GI) disorders including diarrhoea (15.7%) and nausea (13.9%). These GI adverse reactions were mostly mild to moderate in severity, with 0.3% of diarrhoea and 0.3% of nausea reported as being severe. These adverse reactions generally occurred within the first 2 weeks of treatment and usually resolved within 4 weeks. The other most commonly reported adverse reactions included upper respiratory tract infections (8.4%), headache (7.9%), and tension headache (7.2%). Overall, most adverse reactions were considered to be mild or moderate in severity.

The most common adverse reactions leading to discontinuation during the first 16 weeks of treatment were diarrhoea (1.7%), and nausea (1.5%). The overall incidence of serious adverse reactions was low and did not indicate any specific system organ involvement.

Hypersensitivity reactions were uncommonly observed in apremilast clinical studies (see section 4.3).

Tabulated list of adverse reactions
The adverse reactions observed in patients treated with apremilast are listed below by system organ class (SOC) and frequency for all adverse reactions. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The adverse drug reactions were determined based on data from the apremilast clinical development programme. The frequencies of adverse drug reactions are those reported in the apremilast arms of the four Phase III studies in PsA (n = 1945) or the two Phase III studies in PSOR (n=1184) (highest frequency from either data pool is represented in Table 2).
Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

Table 2. Summary of adverse reactions in psoriatic arthritis (PsA) and/or psoriasis (PSOR)

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Bronchitis
		Upper respiratory tract infection
		Nasopharyngitis*
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Common	Decreased appetite*
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Common	Migraine*
		Tension headache*
		Headache*

System Organ Class	Frequency	Adverse reaction
Respiratory, thoracic, and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very Common	Diarrhoea*
		Nausea*
	Common	Vomiting*
		Dyspepsia
		Frequent bowel movements
		Upper abdominal pain *
		Gastroesophageal reflux disease
	Uncommon	Gastrointestinal haemorrhage
Skin and subcutaneous tissue disorders	Uncommon	Rash
Musculoskeletal and connective tissue disorders	Common	Back pain*
General disorders and administrative site conditions	Common	Fatigue
Investigations	Uncommon	Weight decrease

*At least one of these adverse reactions was reported as serious

Description of selected adverse reactions

Body weight loss
Patient weight was measured routinely in clinical studies. The mean observed weight loss in patients treated for up to 52 weeks with apremilast was 1.99 kg. A total of 14.3% of patients receiving apremilast had observed weight loss between 5-10% while 5.7% of the patients receiving apremilast had observed weight loss greater than 10%. None of these patients had overt clinical consequences resulting from weight loss. A total of 0.1% of patients treated with apremilast discontinued due to adverse reaction of weight decreased.

Please see additional warning in section 4.4 for patients who are underweight at beginning of treatment.

Depression
During the placebo-controlled period of the phase III clinical trials PSOR, 1.2% (14/1184) of patients treated with apremilast reported depression compared to 0.5% (2/418) treated with placebo. None of these reports of depression was serious or led to study discontinuation.

Special populations

Elderly patients
No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

Patients with hepatic impairment
The safety of apremilast was not evaluated in PsA or PSOR patients with hepatic impairment.

Patients with renal impairment
In the PsA or PSOR clinical studies, the safety profile observed in patients with mild renal impairment was comparable to patients with normal renal function. The safety of apremilast was not evaluated in PsA or PSOR patients with moderate or severe renal impairment in the clinical studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Apremilast was studied in healthy subjects at a maximum total daily dose of 100 mg (given as 50 mg BID) for 4.5 days without evidence of dose limiting toxicities. In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment is instituted. In the event of overdose, symptomatic and supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosupressants, selective immunosuppressants, ATC code: L04AA32

Mechanism of action
Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10.These pro- and anti-inflammatory mediators have been implicated in psoriatic arthritis and psoriasis.

Pharmacodynamics effects
In clinical studies in patients with psoriatic arthritis, apremilast significantly modulated, but did not fully inhibit, plasma protein levels of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, MMP-3, and TNF-α. After 40 weeks of treatment with apremilast, there was a decrease in plasma protein levels of IL-17 and IL-23, and an increase in IL-10. In clinical trials in patients with psoriasis, apremilast decreased lesional skin epidermal thickness, inflammatory cell infiltration, and expression of pro-inflammatory genes, including those for inducible nitric oxide synthase (iNOS), IL-12/IL-23p40, IL-17A, IL-22 and IL-8.

Apremilast administered at doses of up to 50 mg BID did not prolong the QT interval in healthy subjects.

Clinical trials experience

Psoriatic Arthritis

The safety and efficacy of apremilast were evaluated in 3 multi-center, randomized, double-blind, placebo-controlled studies (Studies PALACE 1, PALACE 2, and PALACE 3) of similar design in adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior treatment with small molecule or biologic DMARDs. A total of 1493 patients were randomised and treated with either placebo, apremilast 20 mg or apremilast 30 mg given orally twice daily.

Patients in these studies had a diagnosis of PsA for at least 6 months. One qualifying psoriatic skin lesion (at least 2 cm in diameter) was also required in PALACE 3. Apremilast was used as a monotherapy (34.8%) or in combination with stable doses of small molecule DMARDs (65.2%). Patients received apremilast in

combination with one or more of the following: methotrexate (MTX, ≤ 25 mg/week, 54.5%), sulfasalazine (SSZ, ≤ 2 g/day, 9.0%), and leflunomide (LEF; ≤ 20 mg/day, 7.4%). Concomitant treatment with biologic DMARDs, including TNF blockers, was not allowed. Patients with each subtype of PsA were enrolled in the 3 studies, including symmetric polyarthritis (62.0%), asymmetric oligoarthritis (26.9%), distal interphalangeal (DIP) joint arthritis (6.2%), arthritis mutilans (2.7%), and predominant spondylitis (2.1%). Patients with pre-existing enthesopathy (63%) or pre-existing dactylitis (42%) were enrolled. A total of 76.4% of patients were previously treated with only small-molecule DMARDs and 22.4% of patients were previously treated with biologic DMARDs, which includes 7.8% who had a therapeutic failure with a prior biologic DMARD. The median duration of PsA disease was 5 years.
Based on the study design, patients whose tender and swollen joint counts had not improved by at least 20% were considered non-responders at Week 16. Placebo patients who were considered non-responders were re-randomized 1:1 in a blinded fashion to either apremilast 20 mg twice daily or 30 mg twice daily. At Week 24, all remaining placebo-treated patients were switched to either apremilast 20 or 30 mg BID.
The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16.

Treatment with apremilast resulted in significant improvements in the signs and symptoms of PsA, as assessed by the ACR 20 response criteria compared to placebo at Weeks 16. The proportion of patients with ACR 20/50/70 (responses in Studies PALACE 1, PALACE 2 and PALACE 3, and the pooled data for studies PALACE 1, PALACE 2 and PALACE 3) for apremilast 30 mg twice daily at Week 16 are shown in Table 3. ACR 20/50/70 responses were maintained at Week 24.

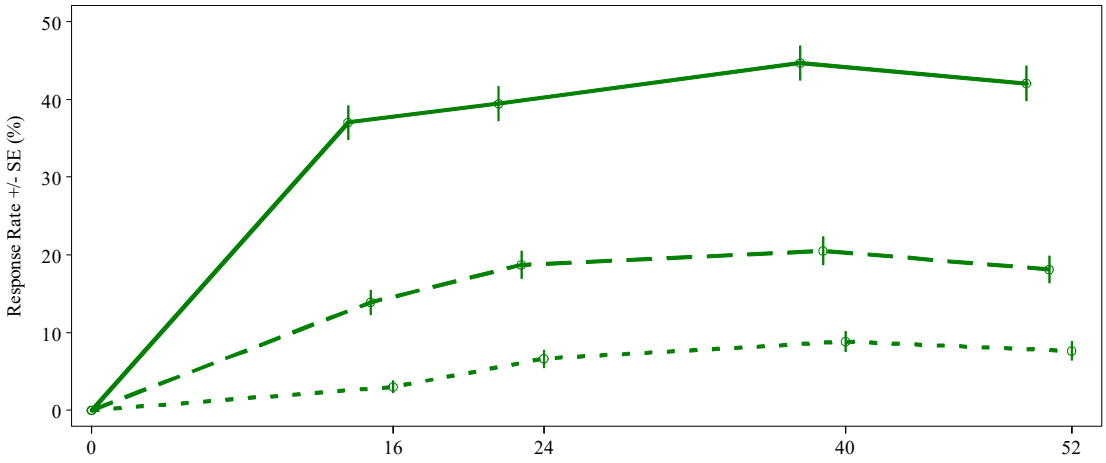
Among patients who were initially randomized to apremilast 30 mg twice daily treatment, ACR 20/50/70 response rates were maintained through Week 52 in the pooled Studies PALACE 1, PALACE 2 and PALACE 3 (Figure 1).

Table 3. Proportion of patients with ACR responses in studies PALACE 1, PALACE 2 and PALACE 3 and pooled studies at Week 16

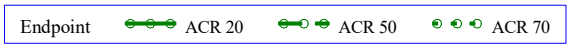
	PALACE 1		**PALACE 2**		**PALACE 3**		**POOLED**	
N[a]	**Placebo +/- DMARDs N=168**	**Apremilast 30 mg BID +/- DMARDs N=168**	**Placebo +/- DMARDs N=159**	**Apremilast 30 mg BID +/- DMARDs N=162**	**Placebo +/- DMARDs N=169**	**Apremilast 30 mg BID +/- DMARDs N=167**	**Placebo +/- DMARDs N=496**	**Apremilast 30 mg BID +/- DMARDs N=497**
ACR 20[a]								
Week 16	19.0%	38.1%**	18.9%	32.1%*	18.3%	40.7%**	18.8%	37.0%**
ACR 50								
Week 16	6.0%	16.1%*	5.0%	10.5%	8.3%	15.0%	6.5%	13.9%**
ACR 70								
Week 16	1.2%	4.2%	0.6%	1.2%	2.4%	3.6%	1.4%	3.0%

*p ≤ 0.01 for apremilast vs. placebo.
**p ≤ 0.001 for apremilast vs. placebo
[a] N is the number of patients as randomized and treated.

Figure 1 Proportion of ACR 20/50/70 responders through Week 52 in the pooled analysis of studies PALACE 1, PALACE 2 and PALACE 3 (NRI*)



Endpoint	n/m (%)	n/m (%)	n/m (%)	n/m (%)
ACR 20	184/497 (37.0)	196/497 (39.4)	222/497 (44.7)	209/497 (42.1)
ACR 50	69/497 (13.9)	93/497 (18.7)	102/497 (20.5)	90/497 (18.1)
ACR 70	15/497 (3.0)	33/497 (6.6)	44/497 (8.9)	38/497 (7.6)



*NRI: None responder imputation. Subjects who discontinued early prior to the time point and subjects who did not have sufficient data for a definitive determination of response status at the time point are counted as non-responders.

Among 497 patients initially randomized to apremilast 30 mg twice daily, 375 (75%) patients were still on this treatment on Week 52. In these patients, ACR 20/50/70 responses at Week 52 were of 57%, 25%, and 11% respectively.

Responses observed in the apremilast treated group were similar in patients receiving and not receiving concomitant DMARDs, including MTX. Patients previously treated with DMARDs or biologics who received apremilast achieved a greater ACR 20 response at Week 16 than patients receiving placebo.

Similar ACR responses were observed in patients with different PsA subtypes, including DIP. The number of patients with arthritis mutilans and predominant spondylitis subtypes was too small to allow meaningful assessment.

In PALACE 1, PALACE 2 and PALACE 3, improvements in Disease Activity Scale (DAS) 28 C-reactive protein (CRP) and in the proportion of patients achieving a modified PsA response criteria (PsARC) were greater in the apremilast group, compared to placebo at Week 16 (nominal p-value $p \leq 0.0004$, p-value ≤ 0.0017, respectively). These improvements were maintained at Week 24. Among patients who remained on the apremilast treatment to which they were randomized at study start, DAS28(CRP) score and PsARC response were maintained through Week 52.

At Weeks 16 and 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) and in the skin manifestations of psoriasis were seen in the apremilast-treated patients. Among patients who remained on the apremilast treatment to which they were randomized at study start, these improvements were maintained through Week 52.

Physical function and health-related quality of life

Apremilast-treated patients demonstrated statistically significant improvement in physical function, as assessed by the disability index of the health assessment questionnaire (HAQ-DI) change from baseline,

compared to placebo at Weeks 16 in PALACE 1, PALACE 2 and PALACE 3 and in the pooled studies Improvement in HAQ-DI scores was maintained at Week 24.

Among patients who were initially randomized to apremilast 30 mg twice daily treatment, the change from baseline in the HAQ-DI score at week 52 was -0.333 in the apremilast 30 mg twice daily group in a pooled analysis of the open label phase of studies PALACE 1, PALACE 2 and PALACE 3.

In studies PALACE 1, PALACE 2 and PALACE 3, significant improvements were demonstrated in health-related quality of life, as measured by the changes from baseline in the physical functioning (PF) domain of the Short Form Health Survey version 2 (SF-36v2), and in the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-fatigue) scores in patients treated with apremilast compared to placebo at Weeks 16 and 24. Among patients who remained on the apremilast treatment, to which they were initially randomized at study start, improvement in physical function and FACIT- fatigue was maintained through Week 52.

Psoriasis
The safety and efficacy of apremilast were evaluated in two multicenter, randomized, double-blind, placebo-controlled studies (Studies ESTEEM 1 and ESTEEM 2) which enrolled a total of 1257 patients with moderate to severe plaque psoriasis who had a body surface area (BSA) involvement of ≥ 10%, Psoriasis Area and Severity Index (PASI) score ≥ 12, static Physician Global Assessment (sPGA) of ≥ 3 (moderate or severe), and who were candidates for phototherapy or systemic therapy.

These studies had a similar design through Week 32. In both studies, patients were randomized 2:1 to apremilast 30 mg BID or placebo for 16 weeks (placebo-controlled phase) and from Weeks 16-32, all patients received apremilast 30 mg BID (maintenance phase). During the Randomized Treatment Withdrawal Phase (Weeks 32-52), patients originally randomized to apremilast who achieved at least a 75% reduction in their PASI score (PASI-75) (ESTEEM 1) or a 50% reduction in their PASI score (PASI-50) (ESTEEM 2) were re-randomized at Week 32 to either placebo or apremilast 30 mg BID. Patients who were re-randomized to placebo and who lost PASI-75 response (ESTEEM 1) or lost 50% of the PASI improvement at Week 32 compared to baseline (ESTEEM 2) were retreated with apremilast 30 mg BID. Patients who did not achieve the designated PASI response by Week 32, or who were initially randomized to placebo, remained on apremilast until Week 52. The use of low potency topical corticosteroids on the face, axillae, and groin, coal tar shampoo and/or salicylic acid scalp preparations was permitted throughout the studies. In addition, at Week 32, subjects who did not achieve a PASI-75 response in ESTEEM 1, or a PASI-50 response in ESTEEM 2, were permitted to use topical psoriasis therapies and/or phototherapy in addition to apremilast 30 mg BID treatment.

In both studies, the primary endpoint was the proportion of patients who achieved PASI-75 at Week 16. The major secondary endpoint was the proportion of patients who achieved a sPGA score of clear (0) or almost clear (1) at Week 16.

The mean baseline PASI score was 19.07 (median 16.80), and the proportion of patients with sPGA score of 3 (moderate) and 4 (severe) at baseline was 70.0% and 29.8%, respectively with a mean baseline BSA involvement of 25.19% (median 21.0%). Approximately 30% of all patients had received prior phototherapy and 54% had received prior conventional systemic and/or biologic therapy for the treatment of psoriasis (including treatment failures), with 37% receiving prior conventional systemic therapy and 30% receiving prior biologic therapy. Approximately one-third of patients had not received prior phototherapy, conventional systemic or biologic therapy. A total of 18% of patients had a history of psoriatic arthritis.

The proportion of patients achieving PASI-50, -75 and -90 responses, and sPGA score of clear (0) or almost clear (1), are presented in Table 4 below. Treatment with apremilast resulted in significant improvement in moderate to severe plaque psoriasis as demonstrated by the proportion of patients with PASI-75 response at Week 16, compared to placebo. Clinical improvement measured by sPGA, PASI-50 and PASI-90 responses were also demonstrated at Week 16. In addition, apremilast demonstrated a treatment benefit across multiple manifestations of psoriasis including pruritus, nail disease, scalp involvement and quality of life measures.

Table 4. Clinical response at week 16 in studies ESTEEM 1 and ESTEEM 2 (FAS [a], LOCF[b])

	ESTEEM 1		ESTEEM 2	
	Placebo	**30 mg BID APR***	**Placebo**	**30 mg BID APR***
N	282	562	137	274
PASI[c] 75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA[d] of Clear or Almost Clear, n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)
PASI 50, n (%)	48 (17.0)	330 (58.7)	27 (19.7)	152 (55.5)
PASI 90, n (%)	1 (0.4)	55 (9.8)	2 (1.5)	24 (8.8)
Percent Change BSA[e] (%) mean± SD	- 6.9 ± 38.95	- 47.8 ± 38.48	- 6.1 ± 47.57	-48.4 ± 40.78
Change in Pruritus VAS[f] (mm), mean± SD	- 7.3 ± 27.08	- 31.5 ± 32.43	- 12.2 ± 30.94	- 33.5 ±35.46
Change in DLQI[g], mean± SD	- 2.1 ± 5.69	- 6.6 ± 6.66	-2.8 ± 7.22	-6.7 ± 6.95
Change in SF-36 MCS [h], mean± SD	- 1.02 ± 9.161	2.39 ± 9.504	0.00 ±10.498	2.58 ± 10.129

* p< 0.0001 for apremilast vs placebo, except for ESTEEM 2 PASI 90 and Change in SF-36 MCS where p=0.0042 and p=0.0078, respectively.
[a] FAS = Full Analysis Set
[b] LOCF= Last Observation Carried forward
[c] PASI = Psoriasis Area and Severity Index
[d] sPGA = Static Physician Global Assessment
[e] BSA = Body Surface Area
[f] VAS = Visual Analog Scale; 0 = best, 100 = worst
[g] DLQI = Dermatology Life Quality Index; 0 = best, 30 = worst
[h] SF-36 MCS = Medical Outcome Study Short Form 36-Item Health Survey, Mental Component Summary

The clinical benefit of apremilast was demonstrated across multiple subgroups defined by baseline demographics and baseline clinical disease characteristics (including psoriasis disease duration and patients with a history of psoriatic arthritis). The clinical benefit of apremilast was also demonstrated regardless of prior psoriasis medication usage and response to prior psoriasis treatments. Similar response rates were observed across all weight ranges.

Response to apremilast was rapid, with significantly greater improvements in the signs and symptoms of psoriasis, including PASI, skin discomfort/pain and pruritus, compared to placebo by Week 2. In general, PASI responses were achieved by Week 16 and were maintained through Week 32.

In both studies, the mean percent improvement in PASI from baseline remained stable during the Randomized Treatment Withdrawal Phase for patients re-randomized to apremilast at Week 32 (Table 5).

Table 5. Persistence of effect among subjects randomized to APR 30 BID at Week 0 and re-randomized to APR 30 BID at Week 32 to Week 52

		ESTEEM 1	ESTEEM 2
	Time Point	**Patients who achieved PASI-75 at Week 32**	**Patients who achieved PASI-50 at Week 32**
Percent Change in PASI from baseline, mean (%) ± SD[a]	Week 16	-77.7 ± 20.30	-69.7 ± 24.23
	Week 32	-88 ± 8.30	-76.7 ± 13.42

	Time Point	ESTEEM 1	ESTEEM 2
		Patients who achieved PASI-75 at Week 32	Patients who achieved PASI-50 at Week 32
	Week 52	-80.5 ± 12.60	-74.4 ± 18.91
Change in DLQI from baseline, mean± SD[a]	Week 16	-8.3 ± 6.26	-7.8 ± 6.41
	Week 32	-8.9 ± 6.68	-7.7 ± 5.92
	Week 52	-7.8 ± 5.75	-7.5 ± 6.27
Proportion of subjects with Scalp Psoriasis PGA (ScPGA) 0 or 1, n/N (%)[b]	Week 16	40/48 (83.3)	21/37 (56.8)
	Week 32	39/48 (81.3)	27/37 (73.0)
	Week 52	35/48 (72.9)	20/37 (54.1)

[a] Includes subjects re-randomized to APR 30 BID at Week 32 with a baseline value and a post-baseline value at the evaluated study week.
[b] N is based on subjects with moderate or greater scalp psoriasis at baseline who were re-randomized to APR 30 BID at Week 32. Subjects with missing data were counted as nonresponders.

In Study ESTEEM 1, approximately 61% of patients re-randomized to apremilast at Week 32 had a PASI-75 response at Week 52. Of the patients with at least a PASI-75 response who were re-randomized to placebo at Week 32 during a Randomized Treatment Withdrawal Phase, 11.7% were PASI-75 responders at Week 52. The median time to loss of PASI-75 response among the patients re-randomized to placebo was 5.1 weeks.

In Study ESTEEM 2, approximately 80.3% of patients re-randomized to apremilast at Week 32 had a PASI-50 response at Week 52. Of the patients with at least a PASI-50 response who were re-randomized to placebo at Week 32, 24.2% were PASI-50 responders at Week 52. The median time to loss of 50% of their Week 32 PASI improvement was 12.4 weeks.

After randomized withdrawal from therapy at Week 32, approximately 70% of patients in Study ESTEEM 1, and 65.6% of patients in Study ESTEEM 2, regained PASI-75 (ESTEEM 1) or PASI-50 (ESTEEM 2) responses after re-initiation of apremilast treatment. Due to the study design the duration of re-treatment was variable, and ranged from 2.6 to 22.1 weeks.

In Study ESTEEM 1, patients randomized to apremilast at the start of the study who did not achieve a PASI-75 response at Week 32 were permitted to use concomitant topical therapies and/or UVB phototherapy between Weeks 32 to 52. Of these patients, 12% achieved a PASI-75 response at Week 52 with apremilast plus topical and/or phototherapy treatment.

In Studies ESTEEM 1 and ESTEEM 2, significant improvements (reductions) in nail psoriasis, as measured by the mean percent change in Nail Psoriasis Severity Index (NAPSI) from baseline, were observed in patients receiving apremilast compared to placebo-treated patients at Week 16 ($p< 0.0001$ and $p=0.0052$, respectively). Further improvements in nail psoriasis were observed at Week 32 in patients continuously treated with apremilast.

In Studies ESTEEM 1 and ESTEEM 2, significant improvements in scalp psoriasis of at least moderate severity (≥3), measured by the proportion of patients achieving Scalp Psoriasis Physician's Global Assessment (ScPGA) of clear (0) or minimal (1) at Week 16, were observed in patients receiving apremilast compared to placebo-treated patients ($p< 0.0001$ for both studies). The improvements were generally maintained in subjects who were re-randomized to Otezla at Week 32 through Week 52 (Table 5).

In Studies ESTEEM 1 and ESTEEM 2, significant improvements in quality of life as measured by the Dermatology Life Quality Index (DLQI) and the SF-36v2MCS were demonstrated in patients receiving apremilast compared with placebo-treated patients (Table 4). Improvements in DLQI were maintained through Week 52 in subjects who were re-randomized to apremilast at Week 32 (Table 5). In addition, in Study ESTEEM 1, significant improvement in the Work Limitations Questionnaire (WLQ-25) Index was achieved in patients receiving apremilast compared to placebo.

5.2 Pharmacokinetic properties

Absorption
Apremilast is well absorbed with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2.5 hours. Apremilast pharmacokinetics are linear, with a dose-proportional increase in systemic exposure in the dose range of 10 to 100 mg daily. Accumulation is minimal when apremilast is administered once daily and approximately 53% in healthy subjects and 68% in patients with psoriasis when administered twice daily. Co-administration with food does not alter the bioavailability therefore, apremilast can be administered with or without food.

Distribution
Human plasma protein binding of apremilast is approximately 68%. The mean apparent volume of distribution (Vd) is 87 L, indicative of extravascular distribution.

Biotransformation
Apremilast is extensively metabolised by both CYP and non-CYP mediated pathways including oxidation, hydrolysis, and conjugation, suggesting inhibition of a single clearance pathway is not likely to cause a marked drug-drug interaction. Oxidative metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6. Apremilast is the major circulating component following oral administration. Apremilast undergoes extensive metabolism with only 3% and 7% of the administered parent compound recovered in urine and faeces, respectively. The major circulating inactive metabolite is the glucuronide conjugate of *O*-demethylated apremilast (M12). Consistent with apremilast being a substrate of CYP3A4, apremilast exposure is decreased when administered concomitantly with rifampicin, a strong inducer of CYP3A4.

In vitro, apremilast is not an inhibitor or inducer of cytochrome P450 enzymes. Hence, apremilast co-administered with substrates of CYP enzymes is unlikely to affect the clearance and exposure of active substances that are metabolised by CYP enzymes.

In vitro, apremilast is a substrate, and a weak inhibitor of P-glycoprotein (IC50>50µM), however clinically relevant drug interactions mediated via P-gp are not expected to occur.

In vitro, apremilast has little to no inhibitory effect (IC50>10µM) on Organic Anion Transporter (OAT)1 and OAT3, Organic Cation Transporter (OCT)2, Organic Anion Transporting Polypeptide (OATP)1B1 and OATP1B3, or breast cancer resistance protein (BCRP) and is not a substrate for these transporters. Hence, clinically relevant drug-drug interactions are unlikely when apremilast is co-administered with drugs that are substrates or inhibitors of these transporters.

Elimination
The plasma clearance of apremilast is on average about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 9 hours. Following oral administration of radiolabelled apremilast, about 58% and 39% of the radioactivity is recovered in urine and faeces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and faeces, respectively.

Elderly patients
Apremilast was studied in young and elderly healthy subjects. The exposure in elderly subjects (65 to 85 years of age) is about 13% higher in AUC and about 6% higher in C_{max} for apremilast than that in young subjects (18 to 55 years of age). There is limited pharmacokinetic data in subjects over 75 years of age in clinical trials. No dosage adjustment is necessary for elderly patients.

Renal impairment
There is no meaningful difference in the PK of apremilast between mild or moderate renal impaired subjects and matched healthy subjects (N=8 each). The results support that no dose adjustment is needed in patients with mild and moderate renal impairment. Reduce apremilast dose to 30 mg once daily in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2 or CLcr < 30 mL/min). In 8 subjects with severe renal impairment to whom a single dose of 30 mg apremilast was administered, the AUC and C_{max} of apremilast increased by approximately 89% and 42%, respectively.

Hepatic impairment
The pharmacokinetics of apremilast and its major metabolite M12 are not affected by moderate or severe hepatic impairment. No dose adjustment is necessary for patients with hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safetypharmacology and repeated dose toxicity. There is no evidencefor immunotoxic, dermal irritation, or phototoxic potential.

Fertility and early embryonic development
In a male mouse fertility study, apremilast at oral dosages of 1, 10, 25, and 50 mg/kg/day produced no effects on male fertility; the no observed adverse effect level (NOAEL) for male fertility was greater than 50 mg/kg/day 3-fold clinical exposure).

In a combined female mouse fertility and embryo-fetal developmental toxicity study with oral dosages of 10, 20, 40, and 80 mg/kg/day, a prolongation of oestrous cycles and increased time to mating were observed at 20 mg/kg/day and above; despite this, all mice mated and pregnancy rates were unaffected. The no observed effect level (NOEL) for female fertility was 10 mg/kg/day (1.0-fold clinical exposure).

Embryo-fetal development
In a combined female mouse fertility and embryo-fetal developmental toxicity study with oral dosages of 10, 20, 40, and 80 mg/kg/day, absolute and/or relative heart weights of maternal animals were increased at 20, 40, and 80 mg/kg/day. Increased numbers of early resorptions and reduced numbers of ossified tarsals were observed at 20, 40, and 80 mg/kg/day. Reduced fetal weights and retarded ossification of the supraoccipital bone of the skull were observed at 40 and 80 mg/kg/day. The maternal and developmental NOEL in the mouse was 10 mg/kg/day (1.3-fold clinical exposure).
In a monkey embryo-fetal developmental toxicity study, oral dosages of 20, 50, 200, and 1000 mg/kg/day resulted in a dose-related increase in prenatal loss (abortions) at dosages of 50 mg/kg/day and above; no test article-related effect in prenatal loss was observed at 20 mg/kg/day (1.4-fold clinical exposure).

Pre- and post-natal development
In a pre- and postnatal study, apremilast was administered orally to pregnant female mice at dosages of 10, 80 and 300 mg/kg/day from gestation day (GD) 6 to Day 20 of lactation. Reductions in maternal body weight and weight gain, and one death associated with difficulty in delivering pups were observed at 300 mg/kg/day. Physical signs of maternal toxicity associated with delivering pups were also observed in one mouse at each of 80 and 300 mg/kg/day. Increased peri- and postnatal pup deaths and reduced pup body weights during the first week of lactation were observed at ≥ 80 mg/kg/day (≥ 4.0-fold clinical exposure). There were no apremilast-related effects on duration of pregnancy, number of pregnant mice at the end of the gestation period, number of mice that delivered a litter, or any developmental effects in the pups beyond postnatal day 7. It is likely that pup developmental effects observed during the first week of the postnatal period were related to the apremilast-related pup toxicity (decreased pup weight and viability) and/or lack of maternal care (higher incidence of no milk in the stomach of pups). All developmental effects were observed during the first week of the postnatal period; no apremilast-related effects were seen during the remaining pre- and post-weaning periods, including sexual maturation, behavioural, mating, fertility and uterine parameters. The NOEL in the mouse for maternal toxicity and F1 generation was 10 mg/kg/day (1.3-fold clinical AUC).

Carcinogenicity studies
Carcinogenicity studies in mice and rats showed no evidence of carcinogenicity related to treatment with apremilast.

Genotoxicity studies
Apremilast is not genotoxic. Apremilast did not induce mutations in an Ames assay or chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. Apremilast was not clastogenic in an in vivo mouse micronucleus assay at doses up to 2000 mg/kg/day.

Other studies
There is no evidence for immunotoxic, dermal irritation, or phototoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate.

Film-coating
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide red (E172).

The 20 mg tablets also contain iron oxide yellow (E172).

The 30 mg tablets also contain iron oxide yellow (E172) and iron oxide black(E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

The treatment initiation pack contains 27 film- coated tablets (4 x10 mg, 4x 20 mg, 19 x 30 mg).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/981/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 January 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Otezla 30 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30 mg of apremilast.

Excipient(s) with known effect:

Each film-coated tablet contains 171 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Beige, diamond shaped 30 mg film-coated tablet of 12 mm length with “APR” engraved on one side and “30” on the opposite side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Psoriatic arthritis
Otezla, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy (see section 5.1).

Psoriasis
Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

4.2 Posology and method of administration

Treatment with Otezla should be initiated by specialists experienced in the diagnosis and treatment of psoriasis or psoriatic arthritis.

Posology
The recommended dose of Otezla is 30 mg twice daily taken orally, morning and evening, approximately 12 hours apart, with no food restrictions. An initial titration schedule is required as shown below in Table 1. No re-titration is required after initial titration.

Table 1: Dose titration schedule

Day 1	Day2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

If patients miss a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose, the missed dose should not be taken and the next dose should be taken at the regular time.

During pivotal trials the greatest improvement was observed within the first 24 weeks of treatment. If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered. The patient's response to treatment should be evaluated on a regular basis. Clinical experience beyond 52 weeks is not available (see section 5.1).

Special populations

Elderly patients

No dose adjustment is required for this patient population (see sections 4.8 and 5.2).

Patients with renal impairment

No dose adjustment is needed in patients with mild and moderate renal impairment. The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockcroft-Gault equation). For initial dose titration in this group, it is recommended that Otezla be titrated using only the AM schedule listed in Table 1 and the PM doses be skipped (see section 5.2).

Patients with hepatic impairment

No dose adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of apremilast in children aged 0 to 17 years have not been established. No data are available.

Method of administration

Otezla is for oral use. The film-coated tablets should be swallowed whole, and can be taken either with or without food.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Otezla should be dose reduced to 30 mg once daily in patients with severe renal impairment (see sections 4.2 and 5.2).

Patients who are underweight at the start of treatment should have their body weight monitored regularly. In the event of unexplained and clinically significant weight loss, these patients should be evaluated by a medical practitioner and discontinuation of treatment should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of strong cytochrome P450 3A4 (CYP3A4) enzyme inducer, rifampicin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. Therefore, the use of strong CYP3A4 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin and St. John's Wort) with apremilast is not recommended. Co-administration of apremilast with multiple doses of rifampicin resulted in a decrease in apremilast area-under-the-concentration time curve (AUC) and maximum serum concentration (C_{max}) by approximately 72% and 43%, respectively. Apremilast exposure is decreased when administered concomitantly with strong inducers of CYP3A4 (e.g. rifampicin) and may result in reduced clinical response.

In clinical studies, apremilast has been administered concomitantly with topical therapy (including corticosteroids, coal tar shampoo and saliycyilic acid scalp preparations) and UVB phototherapy.

There was no clinically meaningful drug-drug interaction between ketoconazole and apremilast. Apremilast can be co-administered with a potent CYP3A4 inhibitor such as ketoconazole.

There was no pharmacokinetic drug-drug interaction between apremilast and methotrexate in psoriatic arthritis patients. Apremilast can be co-administered with methotrexate.

There was no pharmacokinetic drug-drug interaction between apremilast and oral contraceptives containing ethinyl estradiol and norgestimate. Apremilast can be co-administered with oral contraceptives.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Pregnancy should be excluded before treatment can be initiated. Women of childbearing potential should use an effective method of contraception to prevent pregnancy during treatment.

Pregnancy
There are limited data about the use of apremilast in pregnant women.

Apremilast is contraindicated during pregnancy. Effects of apremilast on pregnancy included embryofetal loss in mice and monkeys, and reduced fetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. No such effects were observed when exposure in animals was at 1.3-fold the clinical exposure (see section 5.3).

Breast-feeding
Apremilast was detected in milk of lactating mice (see section 5.3). It is not known whether apremilast, or its metabolites, are excreted in human milk. A risk to the breastfed infant cannot be excluded, therefore apremilast should not be used during breast-feeding.

Fertility
No fertility data is available in humans. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels 3-fold clinical exposure and in females at exposure levels 1-fold clinical exposure. For pre-clinical fertility data see section 5.3.

4.7 Effects on ability to drive and use machines

Apremilast has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions in Phase III clinical studies have been gastrointestinal (GI) disorders including diarrhoea (15.7%) and nausea (13.9%). These GI adverse reactions were mostly mild to

moderate in severity, with 0.3% of diarrhoea and 0.3% of nausea reported as being severe. These adverse reactions generally occurred within the first 2 weeks of treatment and usually resolved within 4 weeks. The other most commonly reported adverse reactions included upper respiratory tract infections (8.4%), headache (7.9%), and tension headache (7.2%). Overall, most adverse reactions were considered to be mild or moderate in severity.

The most common adverse reactions leading to discontinuation during the first 16 weeks of treatment were diarrhoea (1.7%), and nausea (1.5%). The overall incidence of serious adverse reactions was low and did not indicate any specific system organ involvement.

Hypersensitivity reactions were uncommonly observed in apremilast clinical studies (see section 4.3).

Tabulated list of adverse reactions
The adverse reactions observed in patients treated with apremilast are listed below by system organ class (SOC) and frequency for all adverse reactions. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The adverse drug reactions were determined based on data from the apremilast clinical development programme. The frequencies of adverse drug reactions are those reported in the apremilast arms of the four Phase III studies in PsA (n = 1945) or the two Phase III studies in PSOR (n=1184) (highest frequency from either data pool is represented in Table 2).
Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

Table 2. Summary of adverse reactions in psoriatic arthritis (PsA) and/or psoriasis (PSOR)

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Bronchitis
		Upper respiratory tract infection
		Nasopharyngitis*
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Common	Decreased appetite*
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Common	Migraine*
		Tension headache*
		Headache*
Respiratory, thoracic, and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very Common	Diarrhoea*
		Nausea*
	Common	Vomiting*
		Dyspepsia
		Frequent bowel movements
		Upper abdominal pain *
		Gastroesophageal reflux disease
	Uncommon	Gastrointestinal haemorrhage

System Organ Class	Frequency	Adverse reaction
Skin and subcutaneous tissue disorders	Uncommon	Rash
Musculoskeletal and connective tissue disorders	Common	Back pain*
General disorders and administrative site conditions	Common	Fatigue
Investigations	Uncommon	Weight decrease

*At least one of these adverse reactions was reported as serious

Description of selected adverse reactions

Body weight loss
Patient weight was measured routinely in clinical studies. The mean observed weight loss in patients treated for up to 52 weeks with apremilast was 1.99 kg. A total of 14.3% of patients receiving apremilast had observed weight loss between 5-10% while 5.7% of the patients receiving apremilast had observed weight loss greater than 10%. None of these patients had overt clinical consequences resulting from weight loss. A total of 0.1% of patients treated with apremilast discontinued due to adverse reaction of weight decreased.

Please see additional warning in section 4.4 for patients who are underweight at beginning of treatment.

Depression
During the placebo-controlled period of the phase III clinical trials PSOR, 1.2% (14/1184) of patients treated with apremilast reported depression compared to 0.5% (2/418) treated with placebo. None of these reports of depression was serious or led to study discontinuation.

Special populations

Elderly patients
No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

Patients with hepatic impairment
The safety of apremilast was not evaluated in PsA or PSOR patients with hepatic impairment.

Patients with renal impairment
In the PsA or PSOR clinical studies, the safety profile observed in patients with mild renal impairment was comparable to patients with normal renal function. The safety of apremilast was not evaluated in PsA or PSOR patients with moderate or severe renal impairment in the clinical studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Apremilast was studied in healthy subjects at a maximum total daily dose of 100 mg (given as 50 mg BID) for 4.5 days without evidence of dose limiting toxicities. In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment is instituted. In the event of overdose, symptomatic and supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosupressants, selective immunosuppressants, ATC code: L04AA32

Mechanism of action
Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10.These pro- and anti-inflammatory mediators have been implicated in psoriatic arthritis and psoriasis.

Pharmacodynamics effects
In clinical studies in patients with psoriatic arthritis, apremilast significantly modulated, but did not fully inhibit, plasma protein levels of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, MMP-3, and TNF-α. After 40 weeks of treatment with apremilast, there was a decrease in plasma protein levels of IL-17 and IL-23, and an increase in IL-10. In clinical trials in patients with psoriasis, apremilast decreased lesional skin epidermal thickness, inflammatory cell infiltration, and expression of pro-inflammatory genes, including those for inducible nitric oxide synthase (iNOS), IL-12/IL-23p40, IL-17A, IL-22 and IL-8.

Apremilast administered at doses of up to 50 mg BID did not prolong the QT interval in healthy subjects.

Clinical trials experience

Psoriatic Arthritis

The safety and efficacy of apremilast were evaluated in 3 multi-center, randomized, double-blind, placebo-controlled studies (Studies PALACE 1, PALACE 2, and PALACE 3) of similar design in adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior treatment with small molecule or biologic DMARDs. A total of 1493 patients were randomised and treated with either placebo, apremilast 20 mg or apremilast 30 mg given orally twice daily.

Patients in these studies had a diagnosis of PsA for at least 6 months. One qualifying psoriatic skin lesion (at least 2 cm in diameter) was also required in PALACE 3. Apremilast was used as a monotherapy (34.8%) or in combination with stable doses of small molecule DMARDs (65.2%). Patients received apremilast in combination with one or more of the following: methotrexate (MTX, ≤ 25 mg/week, 54.5%), sulfasalazine (SSZ, ≤ 2 g/day, 9.0%), and leflunomide (LEF; ≤ 20 mg/day, 7.4%). Concomitant treatment with biologic DMARDs, including TNF blockers, was not allowed. Patients with each subtype of PsA were enrolled in the 3 studies, including symmetric polyarthritis (62.0%), asymmetric oligoarthritis (26.9%), distal interphalangeal (DIP) joint arthritis (6.2%), arthritis mutilans (2.7%), and predominant spondylitis (2.1%). Patients with pre-existing enthesopathy (63%) or pre-exisiting dactylitis (42%) were enrolled. A total of 76.4% of patients were previously treated with only small-molecule DMARDs and 22.4% of patients were previously treated with biologic DMARDs, which includes 7.8% who had a therapeutic failure with a prior biologic DMARD. The median duration of PsA disease was 5 years.
Based on the study design, patients whose tender and swollen joint counts had not improved by at least 20% were considered non-responders at Week 16. Placebo patients who were considered non-responders were re-randomized 1:1 in a blinded fashion to either apremilast 20 mg twice daily or 30 mg twice daily. At Week 24, all remaining placebo-treated patients were switched to either apremilast 20 or 30 mg BID.
The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16.

Treatment with apremilast resulted in significant improvements in the signs and symptoms of PsA, as assessed by the ACR 20 response criteria compared to placebo at Weeks 16. The proportion of patients with ACR 20/50/70 (responses in Studies PALACE 1, PALACE 2 and PALACE 3, and the pooled data for studies PALACE 1, PALACE 2 and PALACE 3) for apremilast 30 mg twice daily at Week 16 are shown in Table 3. ACR 20/50/70 responses were maintained at Week 24.

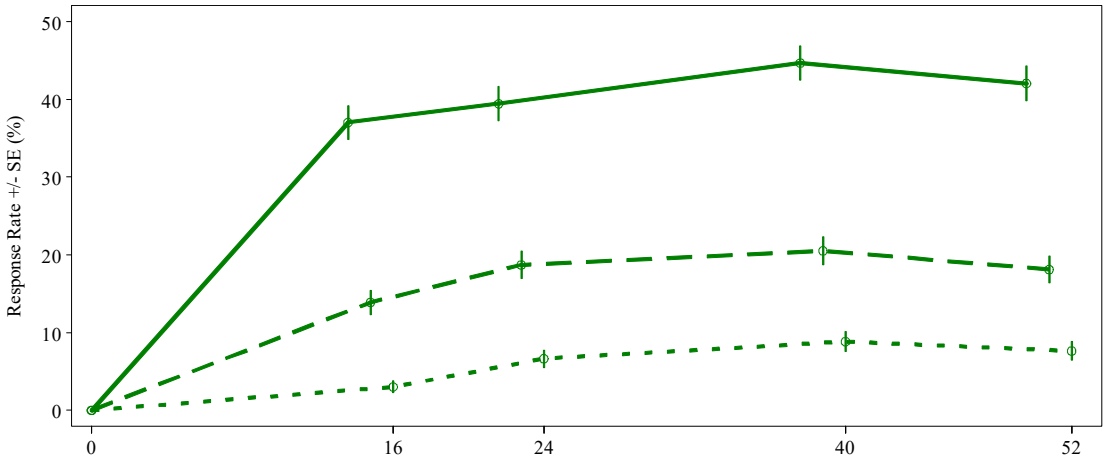
Among patients who were initially randomized to apremilast 30 mg twice daily treatment, ACR 20/50/70 response rates were maintained through Week 52 in the pooled Studies PALACE 1, PALACE 2 and PALACE 3 (Figure 1).

Table 3. Proportion of patients with ACR responses in studies PALACE 1, PALACE 2 and PALACE 3 and pooled studies at Week 16

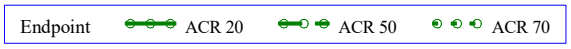
	PALACE 1		PALACE 2		PALACE 3		POOLED	
N[a]	Placebo +/- DMARDs N=168	Apremilast 30 mg BID +/- DMARDs N=168	Placebo +/- DMARDs N=159	Apremilast 30 mg BID +/- DMARDs N=162	Placebo +/- DMARDs N=169	Apremilast 30 mg BID +/- DMARDs N=167	Placebo +/- DMARDs N=496	Apremilast 30 mg BID +/- DMARDs N=497
ACR 20[a]								
Week 16	19.0%	38.1%**	18.9%	32.1%*	18.3%	40.7%**	18.8%	37.0%**
ACR 50								
Week 16	6.0%	16.1%*	5.0%	10.5%	8.3%	15.0%	6.5%	13.9%**
ACR 70								
Week 16	1.2%	4.2%	0.6%	1.2%	2.4%	3.6%	1.4%	3.0%

*$p \leq 0.01$ for apremilast vs. placebo.
**$p \leq 0.001$ for apremilast vs. placebo
[a] N is the number of patients as randomized and treated.

Figure 1 Proportion of ACR 20/50/70 responders through Week 52 in the pooled analysis of studies PALACE 1, PALACE 2 and PALACE 3 (NRI*)



Endpoint	n/m (%)	n/m (%)	n/m (%)	n/m (%)
ACR 20	184/497 (37.0)	196/497 (39.4)	222/497 (44.7)	209/497 (42.1)
ACR 50	69/497 (13.9)	93/497 (18.7)	102/497 (20.5)	90/497 (18.1)
ACR 70	15/497 (3.0)	33/497 (6.6)	44/497 (8.9)	38/497 (7.6)



*NRI: None responder imputation. Subjects who discontinued early prior to the time point and subjects who did not have sufficient data for a definitive determination of response status at the time point are counted as non-responders.

Among 497 patients initially randomized to apremilast 30 mg twice daily, 375 (75%) patients were still on this treatment on Week 52. In these patients, ACR 20/50/70 responses at Week 52 were of 57%, 25%, and 11% respectively.

Responses observed in the apremilast treated group were similar in patients receiving and not receiving concomitant DMARDs, including MTX. Patients previously treated with DMARDs or biologics who received apremilast achieved a greater ACR 20 response at Week 16 than patients receiving placebo.

Similar ACR responses were observed in patients with different PsA subtypes, including DIP. The number of patients with arthritis mutilans and predominant spondylitis subtypes was too small to allow meaningful assessment.

In PALACE 1, PALACE 2 and PALACE 3, improvements in Disease Activity Scale (DAS) 28 C-reactive protein (CRP) and in the proportion of patients achieving a modified PsA response criteria (PsARC) were greater in the apremilast group, compared to placebo at Week 16 (nominal p-value $p \leq 0.0004$, p-value ≤ 0.0017, respectively). These improvements were maintained at Week 24. Among patients who remained on the apremilast treatment to which they were randomized at study start, DAS28(CRP) score and PsARC response were maintained through Week 52.

At Weeks 16 and 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) and in the skin manifestations of psoriasis were seen in the apremilast-treated patients. Among patients who remained on the apremilast treatment to which they were randomized at study start, these improvements were maintained through Week 52.

Physical function and health-related quality of life

Apremilast-treated patients demonstrated statistically significant improvement in physical function, as assessed by the disability index of the health assessment questionnaire (HAQ-DI) change from baseline,

compared to placebo at Weeks 16 in PALACE 1, PALACE 2 and PALACE 3 and in the pooled studies. Improvement in HAQ-DI scores was maintained at Week 24.

Among patients who were initially randomized to apremilast 30 mg twice daily treatment, the change from baseline in the HAQ-DI score at week 52 was -0.333 in the apremilast 30 mg twice daily group in a pooled analysis of the open label phase of studies PALACE 1, PALACE 2 and PALACE 3.

In studies PALACE 1, PALACE 2 and PALACE 3, significant improvements were demonstrated in health-related quality of life, as measured by the changes from baseline in the physical functioning (PF) domain of the Short Form Health Survey version 2 (SF-36v2), and in the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-fatigue) scores in patients treated with apremilast compared to placebo at Weeks 16 and 24. Among patients who remained on the apremilast treatment, to which they were initially randomized at study start, improvement in physical function and FACIT- fatigue was maintained through Week 52.

Psoriasis
The safety and efficacy of apremilast were evaluated in two multicenter, randomized, double-blind, placebo-controlled studies (Studies ESTEEM 1 and ESTEEM 2) which enrolled a total of 1257 patients with moderate to severe plaque psoriasis who had a body surface area (BSA) involvement of ≥ 10%, Psoriasis Area and Severity Index (PASI) score ≥ 12, static Physician Global Assessment (sPGA) of ≥ 3 (moderate or severe), and who were candidates for phototherapy or systemic therapy.

These studies had a similar design through Week 32. In both studies, patients were randomized 2:1 to apremilast 30 mg BID or placebo for 16 weeks (placebo-controlled phase) and from Weeks 16-32, all patients received apremilast 30 mg BID (maintenance phase). During the Randomized Treatment Withdrawal Phase (Weeks 32-52), patients originally randomized to apremilast who achieved at least a 75% reduction in their PASI score (PASI-75) (ESTEEM 1) or a 50% reduction in their PASI score (PASI-50) (ESTEEM 2) were re-randomized at Week 32 to either placebo or apremilast 30 mg BID. Patients who were re-randomized to placebo and who lost PASI-75 response (ESTEEM 1) or lost 50% of the PASI improvement at Week 32 compared to baseline (ESTEEM 2) were retreated with apremilast 30 mg BID. Patients who did not achieve the designated PASI response by Week 32, or who were initially randomized to placebo, remained on apremilast until Week 52. The use of low potency topical corticosteroids on the face, axillae, and groin, coal tar shampoo and/or salicylic acid scalp preparations was permitted throughout the studies. In addition, at Week 32, subjects who did not achieve a PASI-75 response in ESTEEM 1, or a PASI-50 response in ESTEEM 2, were permitted to use topical psoriasis therapies and/or phototherapy in addition to apremilast 30 mg BID treatment.

In both studies, the primary endpoint was the proportion of patients who achieved PASI-75 at Week 16. The major secondary endpoint was the proportion of patients who achieved a sPGA score of clear (0) or almost clear (1) at Week 16.

The mean baseline PASI score was 19.07 (median 16.80), and the proportion of patients with sPGA score of 3 (moderate) and 4 (severe) at baseline was 70.0% and 29.8%, respectively with a mean baseline BSA involvement of 25.19% (median 21.0%). Approximately 30% of all patients had received prior phototherapy and 54% had received prior conventional systemic and/or biologic therapy for the treatment of psoriasis (including treatment failures), with 37% receiving prior conventional systemic therapy and 30% receiving prior biologic therapy. Approximately one-third of patients had not received prior phototherapy, conventional systemic or biologic therapy. A total of 18% of patients had a history of psoriatic arthritis.

The proportion of patients achieving PASI-50, -75 and -90 responses, and sPGA score of clear (0) or almost clear (1), are presented in Table 4 below. Treatment with apremilast resulted in significant improvement in moderate to severe plaque psoriasis as demonstrated by the proportion of patients with PASI-75 response at Week 16, compared to placebo. Clinical improvement measured by sPGA, PASI-50 and PASI-90 responses were also demonstrated at Week 16. In addition, apremilast demonstrated a treatment benefit across multiple manifestations of psoriasis including pruritus, nail disease, scalp involvement and quality of life measures.

Table 4. Clinical response at week 16 in studies ESTEEM 1 and ESTEEM 2 (FAS [a], LOCF[b])

	ESTEEM 1		ESTEEM 2	
	Placebo	**30 mg BID APR***	**Placebo**	**30 mg BID APR***
N	282	562	137	274
PASI[c] 75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA[d] of Clear or Almost Clear, n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)
PASI 50, n (%)	48 (17.0)	330 (58.7)	27 (19.7)	152 (55.5)
PASI 90, n (%)	1 (0.4)	55 (9.8)	2 (1.5)	24 (8.8)
Percent Change BSA[e] (%) mean± SD	- 6.9 ± 38.95	- 47.8 ± 38.48	- 6.1 ± 47.57	-48.4 ± 40.78
Change in Pruritus VAS[f] (mm), mean± SD	- 7.3 ± 27.08	- 31.5 ± 32.43	- 12.2 ± 30.94	- 33.5 ±35.46
Change in DLQI[g], mean± SD	- 2.1 ± 5.69	- 6.6 ± 6.66	-2.8 ± 7.22	-6.7 ± 6.95
Change in SF-36 MCS [h], mean± SD	- 1.02 ± 9.161	2.39 ± 9.504	0.00 ±10.498	2.58 ± 10.129

* p< 0.0001 for apremilast vs placebo, except for ESTEEM 2 PASI 90 and Change in SF-36 MCS where p=0.0042 and p=0.0078, respectively.
[a] FAS = Full Analysis Set
[b] LOCF= Last Observation Carried forward
[c] PASI = Psoriasis Area and Severity Index
[d] sPGA = Static Physician Global Assessment
[e] BSA = Body Surface Area
[f] VAS = Visual Analog Scale; 0 = best, 100 = worst
[g] DLQI = Dermatology Life Quality Index; 0 = best, 30 = worst
[h] SF-36 MCS = Medical Outcome Study Short Form 36-Item Health Survey, Mental Component Summary

The clinical benefit of apremilast was demonstrated across multiple subgroups defined by baseline demographics and baseline clinical disease characteristics (including psoriasis disease duration and patients with a history of psoriatic arthritis). The clinical benefit of apremilast was also demonstrated regardless of prior psoriasis medication usage and response to prior psoriasis treatments. Similar response rates were observed across all weight ranges.

Response to apremilast was rapid, with significantly greater improvements in the signs and symptoms of psoriasis, including PASI, skin discomfort/pain and pruritus, compared to placebo by Week 2. In general, PASI responses were achieved by Week 16 and were maintained through Week 32.

In both studies, the mean percent improvement in PASI from baseline remained stable during the Randomized Treatment Withdrawal Phase for patients re-randomized to apremilast at Week 32 (Table 5).

Table 5. Persistence of effect among subjects randomized to APR 30 BID at Week 0 and re-randomized to APR 30 BID at Week 32 to Week 52

		ESTEEM 1	ESTEEM 2
	Time Point	**Patients who achieved PASI-75 at Week 32**	**Patients who achieved PASI-50 at Week 32**
Percent Change in PASI from baseline, mean (%) ± SD[a]	Week 16	-77.7 ± 20.30	-69.7 ± 24.23
	Week 32	-88 ± 8.30	-76.7 ± 13.42

	Time Point	ESTEEM 1	ESTEEM 2
		Patients who achieved PASI-75 at Week 32	Patients who achieved PASI-50 at Week 32
	Week 52	-80.5 ± 12.60	-74.4 ± 18.91
Change in DLQI from baseline, mean± SD[a]	Week 16	-8.3 ± 6.26	-7.8 ± 6.41
	Week 32	-8.9 ± 6.68	-7.7 ± 5.92
	Week 52	-7.8 ± 5.75	-7.5 ± 6.27
Proportion of subjects with Scalp Psoriasis PGA (ScPGA) 0 or 1, n/N (%)[b]	Week 16	40/48 (83.3)	21/37 (56.8)
	Week 32	39/48 (81.3)	27/37 (73.0)
	Week 52	35/48 (72.9)	20/37 (54.1)

[a] Includes subjects re-randomized to APR 30 BID at Week 32 with a baseline value and a post-baseline value at the evaluated study week.
[b] N is based on subjects with moderate or greater scalp psoriasis at baseline who were re-randomized to APR 30 BID at Week 32. Subjects with missing data were counted as nonresponders.

In Study ESTEEM 1, approximately 61% of patients re-randomized to apremilast at Week 32 had a PASI-75 response at Week 52. Of the patients with at least a PASI-75 response who were re-randomized to placebo at Week 32 during a Randomized Treatment Withdrawal Phase, 11.7% were PASI-75 responders at Week 52. The median time to loss of PASI-75 response among the patients re-randomized to placebo was 5.1 weeks.

In Study ESTEEM 2, approximately 80.3% of patients re-randomized to apremilast at Week 32 had a PASI-50 response at Week 52. Of the patients with at least a PASI-50 response who were re-randomized to placebo at Week 32, 24.2% were PASI-50 responders at Week 52. The median time to loss of 50% of their Week 32 PASI improvement was 12.4 weeks.

After randomized withdrawal from therapy at Week 32, approximately 70% of patients in Study ESTEEM 1, and 65.6% of patients in Study ESTEEM 2, regained PASI-75 (ESTEEM 1) or PASI-50 (ESTEEM 2) responses after re-initiation of apremilast treatment. Due to the study design the duration of re-treatment was variable, and ranged from 2.6 to 22.1 weeks.

In Study ESTEEM 1, patients randomized to apremilast at the start of the study who did not achieve a PASI-75 response at Week 32 were permitted to use concomitant topical therapies and/or UVB phototherapy between Weeks 32 to 52. Of these patients, 12% achieved a PASI-75 response at Week 52 with apremilast plus topical and/or phototherapy treatment.

In Studies ESTEEM 1 and ESTEEM 2, significant improvements (reductions) in nail psoriasis, as measured by the mean percent change in Nail Psoriasis Severity Index (NAPSI) from baseline, were observed in patients receiving apremilast compared to placebo-treated patients at Week 16 ($p< 0.0001$ and $p=0.0052$, respectively). Further improvements in nail psoriasis were observed at Week 32 in patients continuously treated with apremilast.

In Studies ESTEEM 1 and ESTEEM 2, significant improvements in scalp psoriasis of at least moderate severity (≥3), measured by the proportion of patients achieving Scalp Psoriasis Physician's Global Assessment (ScPGA) of clear (0) or minimal (1) at Week 16, were observed in patients receiving apremilast compared to placebo-treated patients ($p< 0.0001$ for both studies). The improvements were generally maintained in subjects who were re-randomized to Otezla at Week 32 through Week 52 (Table 5).

In Studies ESTEEM 1 and ESTEEM 2, significant improvements in quality of life as measured by the Dermatology Life Quality Index (DLQI) and the SF-36v2MCS were demonstrated in patients receiving apremilast compared with placebo-treated patients (Table 4). Improvements in DLQI were maintained through Week 52 in subjects who were re-randomized to apremilast at Week 32 (Table 5). In addition, in Study ESTEEM 1, significant improvement in the Work Limitations Questionnaire (WLQ-25) Index was achieved in patients receiving apremilast compared to placebo.

5.2 Pharmacokinetic properties

Absorption
Apremilast is well absorbed with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2.5 hours. Apremilast pharmacokinetics are linear, with a dose-proportional increase in systemic exposure in the dose range of 10 to 100 mg daily. Accumulation is minimal when apremilast is administered once daily and approximately 53% in healthy subjects and 68% in patients with psoriasis when administered twice daily. Co-administration with food does not alter the bioavailability therefore, apremilast can be administered with or without food.

Distribution
Human plasma protein binding of apremilast is approximately 68%. The mean apparent volume of distribution (Vd) is 87 L, indicative of extravascular distribution.

Biotransformation
Apremilast is extensively metabolised by both CYP and non-CYP mediated pathways including oxidation, hydrolysis, and conjugation, suggesting inhibition of a single clearance pathway is not likely to cause a marked drug-drug interaction. Oxidative metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6. Apremilast is the major circulating component following oral administration. Apremilast undergoes extensive metabolism with only 3% and 7% of the administered parent compound recovered in urine and faeces, respectively. The major circulating inactive metabolite is the glucuronide conjugate of *O*-demethylated apremilast (M12). Consistent with apremilast being a substrate of CYP3A4, apremilast exposure is decreased when administered concomitantly with rifampicin, a strong inducer of CYP3A4.

In vitro, apremilast is not an inhibitor or inducer of cytochrome P450 enzymes. Hence, apremilast co-administered with substrates of CYP enzymes is unlikely to affect the clearance and exposure of active substances that are metabolised by CYP enzymes.

In vitro, apremilast is a substrate, and a weak inhibitor of P-glycoprotein (IC50>50µM), however clinically relevant drug interactions mediated via P-gp are not expected to occur.

In vitro, apremilast has little to no inhibitory effect (IC50>10µM) on Organic Anion Transporter (OAT)1 and OAT3, Organic Cation Transporter (OCT)2, Organic Anion Transporting Polypeptide (OATP)1B1 and OATP1B3, or breast cancer resistance protein (BCRP) and is not a substrate for these transporters. Hence, clinically relevant drug-drug interactions are unlikely when apremilast is co-administered with drugs that are substrates or inhibitors of these transporters.

Elimination
The plasma clearance of apremilast is on average about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 9 hours. Following oral administration of radiolabelled apremilast, about 58% and 39% of the radioactivity is recovered in urine and faeces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and faeces, respectively.

Elderly patients
Apremilast was studied in young and elderly healthy subjects. The exposure in elderly subjects (65 to 85 years of age) is about 13% higher in AUC and about 6% higher in C_{max} for apremilast than that in young subjects (18 to 55 years of age). There is limited pharmacokinetic data in subjects over 75 years of age in clinical trials. No dosage adjustment is necessary for elderly patients.

Renal impairment
There is no meaningful difference in the PK of apremilast between mild or moderate renal impaired subjects and matched healthy subjects (N=8 each). The results support that no dose adjustment is needed in patients with mild and moderate renal impairment. Reduce apremilast dose to 30 mg once daily in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2 or CLcr < 30 mL/min). In 8 subjects with severe renal impairment to whom a single dose of 30 mg apremilast was administered, the AUC and C_{max} of apremilast increased by approximately 89% and 42%, respectively.

Hepatic impairment
The pharmacokinetics of apremilast and its major metabolite M12 are not affected by moderate or severe hepatic impairment. No dose adjustment is necessary for patients with hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safetypharmacology and repeated dose toxicity. There is no evidencefor immunotoxic, dermal irritation, or phototoxic potential.

Fertility and early embryonic development
In a male mouse fertility study, apremilast at oral dosages of 1, 10, 25, and 50 mg/kg/day produced no effects on male fertility; the no observed adverse effect level (NOAEL) for male fertility was greater than 50 mg/kg/day 3-fold clinical exposure).

In a combined female mouse fertility and embryo-fetal developmental toxicity study with oral dosages of 10, 20, 40, and 80 mg/kg/day, a prolongation of oestrous cycles and increased time to mating were observed at 20 mg/kg/day and above; despite this, all mice mated and pregnancy rates were unaffected. The no observed effect level (NOEL) for female fertility was 10 mg/kg/day (1.0-fold clinical exposure).

Embryo-fetal development
In a combined female mouse fertility and embryo-fetal developmental toxicity study with oral dosages of 10, 20, 40, and 80 mg/kg/day, absolute and/or relative heart weights of maternal animals were increased at 20, 40, and 80 mg/kg/day. Increased numbers of early resorptions and reduced numbers of ossified tarsals were observed at 20, 40, and 80 mg/kg/day. Reduced fetal weights and retarded ossification of the supraoccipital bone of the skull were observed at 40 and 80 mg/kg/day. The maternal and developmental NOEL in the mouse was 10 mg/kg/day (1.3-fold clinical exposure).
In a monkey embryo-fetal developmental toxicity study, oral dosages of 20, 50, 200, and 1000 mg/kg/day resulted in a dose-related increase in prenatal loss (abortions) at dosages of 50 mg/kg/day and above; no test article-related effect in prenatal loss was observed at 20 mg/kg/day (1.4-fold clinical exposure).

Pre- and post-natal development
In a pre- and postnatal study, apremilast was administered orally to pregnant female mice at dosages of 10, 80 and 300 mg/kg/day from gestation day (GD) 6 to Day 20 of lactation. Reductions in maternal body weight and weight gain, and one death associated with difficulty in delivering pups were observed at 300 mg/kg/day. Physical signs of maternal toxicity associated with delivering pups were also observed in one mouse at each of 80 and 300 mg/kg/day. Increased peri- and postnatal pup deaths and reduced pup body weights during the first week of lactation were observed at ≥ 80 mg/kg/day (≥ 4.0-fold clinical exposure). There were no apremilast-related effects on duration of pregnancy, number of pregnant mice at the end of the gestation period, number of mice that delivered a litter, or any developmental effects in the pups beyond postnatal day 7. It is likely that pup developmental effects observed during the first week of the postnatal period were related to the apremilast-related pup toxicity (decreased pup weight and viability) and/or lack of maternal care (higher incidence of no milk in the stomach of pups). All developmental effects were observed during the first week of the postnatal period; no apremilast-related effects were seen during the remaining pre- and post-weaning periods, including sexual maturation, behavioural, mating, fertility and uterine parameters. The NOEL in the mouse for maternal toxicity and F1 generation was 10 mg/kg/day (1.3-fold clinical AUC).

Carcinogenicity studies
Carcinogenicity studies in mice and rats showed no evidence of carcinogenicity related to treatment with apremilast.

Genotoxicity studies
Apremilast is not genotoxic. Apremilast did not induce mutations in an Ames assay or chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. Apremilast was not clastogenic in an in vivo mouse micronucleus assay at doses up to 2000 mg/kg/day.

Other studies
There is no evidence for immunotoxic, dermal irritation, or phototoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate.

Film-coating
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide red (E172).

The 30 mg tablets also contain iron oxide yellow (E172) and iron oxide black(E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

PVC/ aluminium foil blisters containing 14 film- coated tablets, in pack sizes of 56 tablets (30 mg) and 168 tablets (30 mg).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/981/002
EU/1/14/981/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 January 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
Middlesex
UB11 1DB
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Wallet card containing 2-week treatment initiation pack

1. NAME OF THE MEDICINAL PRODUCT

Otezla 10 mg film-coated tablets
Otezla 20 mg film-coated tablets
Otezla 30 mg film-coated tablets
apremilast

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg, 20 mg or 30 mg of apremilast.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
Treatment initiation pack
4 film-coated tablets of 10 mg
4 film-coated tablets of 20 mg
19 film-coated tablets of 30 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/981/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Otezla 10 mg
Otezla 20 mg
Otezla 30 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister (Particulars printed directly onto the wallet card with the blank blister sealed inside)

1. NAME OF THE MEDICINAL PRODUCT

Otezla 10 mg tablets
Otezla 20 mg tablets
Otezla 30 mg tablets

apremilast

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Otezla 30 mg film–coated tablets
apremilast

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 30 mg of apremilast.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
56 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/981/002
EU/1/14/981/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Otezla 30 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Otezla 30 mg tablets
apremilast

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Otezla 10 mg film-coated tablets
Otezla 20 mg film-coated tablets
Otezla 30 mg film-coated tablets
Apremilast

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine - because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Otezla is and what it is used for

What Otezla is

Otezla contains the active substance ‘apremilast’. This belongs to a group of medicines called phosphodiesterase 4 inhibitors, which help to reduce inflammation.

What Otezla is used for
Otezla is used to treat adults with the following conditions:
- **Psoriatic arthritis -** if you cannot use another type of medicine called ‘Disease-Modifying Antirheumatic Drugs’ (DMARDs) or when you have tried one of these medicines and it did not work.
- **Moderate to severe plaque psoriasis -** if you cannot use one of the following treatments or when you have tried one of these treatments and it did not work:
  - phototherapy - a treatment where certain areas of skin are exposed to ultraviolet light
  - systemic therapy - a treatment that affects the entire body rather than just one local area, such as ‘ciclosporin’ or ‘methotrexate’.

What psoriatic arthritis is
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis, an inflammatory disease of the skin.

What plaque psoriasis is
Psoriasis is an inflammatory disease of the skin, which can cause red, scaly, thick, itchy, painful patches on your skin and can also affect your scalp and nails.

How Otezla works
Psoriatic arthritis and psoriasis are usually lifelong conditions and there is currently no cure. Otezla works by reducing the activity of an enzyme in the body called 'phosphodiesterase 4', which is involved in the process of inflammation. By reducing the activity of this enzyme, Otezla can help to control the inflammation associated with psoriatic arthritis and psoriasis, and thereby reduce the signs and symptoms of these conditions.

In psoriatic arthritis, treatment with Otezla results in an improvement in swollen and painful joints, and can improve your general physical function.

In psoriasis, treatment with Otezla results in a reduction in psoriatic skin plaques and other signs and symptoms of the disease.

Otezla has also been shown to improve the quality of life in patients with psoriasis or psoriatic arthritis. This means that the impact of your condition on daily activities, relationships and other factors should be less than it was before.

2. What you need to know before you take Otezla

Do not take Otezla:

- if you are allergic to apremilast or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or think you may be pregnant.

Warnings and precautions
Talk to your doctor or pharmacist before taking Otezla.

If your doctor considers you to be underweight, and you observe an unintentional loss of body weight while being treated with Otezla, you should talk to your doctor.
If you have severe kidney problems then the recommended dose of Otezla is 30 mg **once a day (morning dose)**. Your doctor will talk to you about how to increase your dose when you first start taking Otezla.

Children and adolescents
Otezla has not been studied in children and adolescents, therefore it is not recommended for use in children and adolescents aged 17 years and under.

Other medicines and Otezla
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Otezla can affect the way some other medicines work. Also some other medicines can affect the way Otezla works.

In particular, tell your doctor or pharmacist before taking Otezla if you are taking any of the following medicines:

- rifampicin – an antibiotic used for tuberculosis
- phenytoin, phenobarbital and carbamazepine - medicines used in the treatment of seizures or epilepsy
- St John's Wort – a herbal medicine for mild anxiety and depression.

Pregnancy and breast-feeding
There is little information about the effects of Otezla in pregnancy. You should not become pregnant while taking this medicine and should use an effective method of contraception during treatment with Otezla. It is not known if this medicine passes into human milk. You should not use Otezla while breast-feeding.

Tell your doctor if you think you may be pregnant or are planning to have a baby, or if you are breast-feeding or intend to breast-feed.

Driving and using machines
Otezla has no effect on the ability to drive and use machines.

Otezla contains lactose
Otezla contains lactose (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

3. How to take Otezla

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

- When you first start taking Otezla, you will receive a 'treatment initiation pack' which contains all the doses as listed in the table below.
- The 'treatment initiation pack' is clearly labelled to make sure you take the correct tablet at the correct time.
- Your treatment will start at a lower dose and will gradually be increased over the first 6 days of treatment.
- The 'treatment initiation pack' will also contain enough tablets for another 8 days at the recommended dose (Days 7 to 14).
- The recommended dose of Otezla is 30 mg twice a day after the titration phase is complete - one 30 mg dose in the morning and one 30 mg dose in the evening, approximately 12 hours apart, with or without food.
- This is a total daily dose of 60 mg. By the end of Day 6 you will have reached this recommended dose.
- Once the recommended dose has been reached, you will only get the 30 mg tablet strength in your prescribed packs. You will only ever need to go through this stage of gradually increasing your dose once even if you re-start treatment.

Day	Morning Dose	Evening Dose	Total Daily Dose
Day 1	10 mg (pink)	**Do not take a dose**	10 mg
Day 2	10 mg (pink)	10 mg (pink)	20 mg
Day 3	10 mg (pink)	20 mg (brown)	30 mg
Day 4	20 mg (brown)	20 mg (brown)	40 mg
Day 5	20 mg (brown)	30 mg (beige)	50 mg
Day 6 onwards	30 mg (beige)	30 mg (beige)	60 mg

People with kidney problems
If you have severe kidney problems then the recommended dose of Otezla is 30 mg **once a day (morning dose)**. Your doctor will talk to you about how to increase your dose when you first start taking Otezla.

How and when to take Otezla
- Swallow the tablets whole, preferably with water.
- You can take the tablets either with or without food.
- Take Otezla at about the same time each day, one tablet in the morning and one tablet in the evening.
- If your condition has not improved after six months of treatment, you should talk to your doctor.

If you take more Otezla than you should
If you take more Otezla than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack and this leaflet with you.

If you forget to take Otezla
- If you miss a dose of Otezla, take it as soon as you remember. If it is close to the time for your next dose, just skip the missed dose. Take the next dose at your regular time.
- Do not take two doses at the same time.

If you stop taking Otezla
- You should continue taking Otezla until your doctor tells you to stop.
- Do not stop taking Otezla without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than 1 in 10 people)
- diarrhoea
- nausea

Common side effects (may affect up to 1 in 10 people)
- cough
- back pain
- vomiting
- feeling tired
- stomach pain
- loss of appetite
- frequent bowel movements
- difficulty sleeping (insomnia)
- indigestion or heartburn
- headaches, migraines or tension headaches
- upper respiratory tract infections such as cold, runny nose, sinus infection.
- inflammation and swelling of the tubes in your lungs (bronchitis).
- common cold (nasopharyngitis)

Uncommon side effects (may affect up to 1 in 100 people)
- rash
- weight loss
- allergic reaction
- Bleeding in the bowel or in the stomach

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Otezla

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.
- Do not store above 30°C.
- Do not use Otezla if you notice any damage or signs of tampering to the medicine packaging.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Otezla contains

- The active substance is apremilast.
- Each film-coated tablet contains 10 mg of apremilast.
- Each film-coated tablet contains 20 mg of apremilast.
- Each film-coated tablet contains 30 mg of apremilast.

- The other ingredients in the tablet core are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate.
- The film-coating contains polyvinyl alcohol, titanium dioxide (E171), - macrogol, talc, iron oxide red (E172).
- The 20 mg film-coated tablet also contains iron oxide yellow (E172).
- The 30 mg film-coated tablet also contains iron oxide yellow (E172) and iron oxide black (E172).

What Otezla looks like and contents of the pack

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.

Pack sizes
- The treatment initiation pack is a folding wallet containing 27 tablets: 4 x 10 mg tablets, 4 x 20 mg tablets and 19 x 30 mg tablets.
- The one-month standard pack contains 56 x 30 mg tablets.
- The three-month standard pack contains 168 x 30 mg tablets.

Marketing Authorisation Holder and Manufacturer

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for apremilast, the scientific conclusions of CHMP are as follows:

Based on the analysis of cases of gastrointestinal haemorrhages reported in the post-marketing setting and in clinical trials, there is evidence to suggest a causal association with the use of apremilast. This relationship is supported after reviewing the cases in Eudravigilance by the following: compatible temporal association; positive dechallenge in all cases with spontaneous recovery after withdrawal of apremilast and lack of confounding factors (concomitant medication, medical conditions). Moreover, during the placebo-controlled period a higher number of gastrointestinal bleeding was experienced by patients treated with apremilast than with placebo; even when the absolute numbers were low.

Therefore, in view of available data regarding gastrointestinal haemorrhages with the use of apremilast, the PRAC considered that changes to the product information were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for apremilast the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing apremilast is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

APPENDIX 7: CREDIBLEMEDS™ FILTERED QT DRUG LIST

COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CredibleMeds® has reviewed available evidence for the drugs on the following list and place them in one of three designated categories: Known Risk of TdP (KR), Possible Risk of TdP (PR) or have a Conditional Risk of TdP (CR). The full description of these categories can be found on the CredibleMeds.org website.

Generic Name	Brand Name
Abarelix (PR)	Plenaxis
Abiraterone (CR)	Zytiga and others
Aclarubicin (KR)	Aclacin and others
Alfuzosin (PR)	Uroxatral
Alimemazine (Trimeprazine) (PR)	Nedeltran and others
Amantadine (CR)	Symmetrel and others
Amiodarone (KR)	Cordarone and others
Amisulpride (CR)	Barhemsys and others
Amitriptyline (CR)	Elavil (Discontinued 6/13) and others
Amphotericin B (CR)	Fungilin and others
Amsacrine (Acridinyl anisidide) (CR)	Amsidine
Anagrelide (KR)	Agrylin and others
Apalutamide (PR)	Erleada
Apomorphine (PR)	Apokyn and others
Aripiprazole (PR)	Abilify and others
Arsenic trioxide (KR)	Trisenox
Artemether/Lumefantrine (PR)	Coartem
Artenimol/piperaquine (PR)	Eurartesim
Asenapine (PR)	Saphris and others
Astemizole (KR)	Hismanal
Atazanavir (CR)	Reyataz and others
Atomoxetine (PR)	Strattera

Generic Name	Brand Name
Azithromycin (KR)	Zithromax and others
Bedaquiline (PR)	Sirturo
Bendamustine (PR)	Treanda and others
Bendroflumethiazide (Bendrofluazide) (CR)	Aprinox and others
Benperidol (PR)	Anquil and others
Bepridil (KR)	Vascor
Betrixaban (PR)	Bevyxxa
Bortezomib (PR)	Velcade and others
Bosutinib (PR)	Bosulif
Buprenorphine (PR)	Butrans and others
Cabozantinib (PR)	Cometriq
Capecitabine (PR)	Xeloda
Carbetocin (PR)	Pabal and others
Ceritinib (PR)	Zykadia
Cesium Chloride (KR)	Energy Catalyst
Chloral hydrate (CR)	Aquachloral and others
Chloroquine (KR)	Aralen
Chlorpromazine (KR)	Thorazine and others
Chlorprothixene (KR)	Truxal
Cilostazol (KR)	Pletal
Cimetidine (CR)	Tagamet
Ciprofloxacin (KR)	Cipro and others

Generic Name	Brand Name
Cisapride (KR)	Propulsid
Citalopram (KR)	Celexa and others
Clarithromycin (KR)	Biaxin and others
Clofazimine (PR)	Lamprene
Clomipramine (CR)	Anafranil
Clotiapine (PR)	Entumine
Clozapine (PR)	Clozaril and others
Cobimetinib (PR)	Cotellic
Cocaine (KR)	Cocaine
Crizotinib (PR)	Xalkori
Cyamemazine (Cyamepromazine) (PR)	Tercian
Dabrafenib (PR)	Tafinlar
Dasatinib (PR)	Sprycel
Degarelix (PR)	Firmagon and others
Delamanid (PR)	Deltyba
Desipramine (PR)	Pertofrane and others
Deutetrabenazine (PR)	Austedo
Dexmedetomidine (PR)	Precedex and others
Dextromethorphan/Quinidine (PR)	Nuedexta
Diphenhydramine (CR)	Benadryl and others
Disopyramide (KR)	Norpace
Dofetilide (KR)	Tikosyn

If list is printed, check website at www.crediblemeds.org • Please see Disclaimer below • List continued over

Generic Name	Brand Name
Dolasetron (PR)	Anzemet
Domperidone (KR)	Motilium and others
Donepezil (KR)	Aricept
Doxepin (CR)	Sinequan and others
Dronedarone (KR)	Multaq
Droperidol (KR)	Inapsine and others
Efavirenz (PR)	Sustiva
Eliglustat (PR)	Cerdelga
Encorafenib (PR)	Braftovi
Entrectinib (PR)	Rozlytrek
Eperisone (CR)	Myonal and others
Epirubicin (PR)	Ellence and others
Eribulin mesylate (PR)	Halaven
Erythromycin (KR)	E.E.S. and others
Escitalopram (KR)	Cipralex and others
Esomeprazole (CR)	Nexium and others
Ezogabine (Retigabine) (PR)	Potiga and others
Famotidine (CR)	Pepcid and others
Felbamate (PR)	Felbatol
Fingolimod (PR)	Gilenya
Flecainide (KR)	Tambocor and others
Fluconazole (KR)	Diflucan and others
Fluorouracil (5-FU) (PR)	Adrucil and others
Fluoxetine (CR)	Prozac and others
Flupentixol (PR)	Depixol and others
Fluvoxamine (CR)	Faverin and others
Furosemide (frusemide) (CR)	Lasix and others
Galantamine (CR)	Reminyl and others

Generic Name	Brand Name
Garenoxacin (CR)	Geninax
Gatifloxacin (KR)	Tequin
Gemifloxacin (PR)	Factive
Gilteritinib (PR)	Xospata
Glasdegib (PR)	Daurismo
Granisetron (PR)	Kytril and others
Grepafloxacin (KR)	Raxar
Halofantrine (KR)	Halfan
Haloperidol (KR)	Haldol and others
Hydrochlorothiazide (CR)	Apo-Hydro and others
Hydrocodone - ER (PR)	Hysinglaâ„¢ ER and others
Hydroquinidine (Dihydroquinidine) (KR)	Serecor
Hydroxychloroquine (KR)	Plaquenil and others
Hydroxyzine (CR)	Atarax and others
Ibogaine (KR)	
Ibutilide (KR)	Corvert
Iloperidone (PR)	Fanapt and others
Imipramine (Melipramine) (PR)	Tofranil
Indapamide (CR)	Lozol and others
Inotuzumab ozogamicin (PR)	Besponsa
Isradipine (PR)	Dynacirc
Itraconazole (CR)	Sporanox and others
Ivabradine (CR)	Procoralan and others
Ivosidenib (PR)	Tibsovo
Ketanserin (PR)	Sufrexal
Ketoconazole (CR)	Nizoral and others
Lacidipine (PR)	Lacipil and others
Lansoprazole (CR)	Prevacid and others

Generic Name	Brand Name
Lapatinib (PR)	Tykerb and others
Lefamulin (PR)	Xenleta
Lenvatinib (PR)	Lenvima
Leuprolide (Leuprorelin) (PR)	Lupron and others
Levetiracetam (PR)	Keppra
Levofloxacin (KR)	Levaquin and others
Levomepromazine (Methotrimeprazine) (KR)	Nosinan and others
Levomethadone (levamethadone) (PR)	
Levomethadyl acetate (KR)	Orlaam
Levosulpiride (KR)	Lesuride and others
Lithium (PR)	Eskalith and others
Lofexidine (PR)	Lucemyra
Loperamide (CR)	Imodium
Lopinavir/Ritonavir (PR)	Kaletra and others
Lumateperone (PR)	Caplyta
Lurasidone (PR)	Latuda
Maprotiline (PR)	Ludiomil
Meglumine antimoniate (KR)	Glucantime
Melperone (PR)	Bunil and others
Memantine (PR)	Namenda XR
Mesoridazine (KR)	Serentil
Methadone (KR)	Dolophine and others
Metoclopramide (CR)	Reglan and others
Metolazone (CR)	Zytanix and others
Metronidazole (CR)	Flagyl
Mianserin (PR)	Tolvon
Midostaurin (PR)	Rydapt
Mifepristone (PR)	Korlym and others

Generic Name	Brand Name
Mirabegron (PR)	Myrbetriq
Mirtazapine (PR)	Remeron
Moexipril/Hydrochlorothiazide (PR)	Uniretic and others
Moxifloxacin (KR)	Avelox and others
Necitumumab (PR)	Portrazza
Nelfinavir (CR)	Viracept
Nicardipine (PR)	Cardene
Nifekalant (KR)	Shinbit
Nilotinib (PR)	Tasigna
Norfloxacin (PR)	Noroxin and others
Nortriptyline (PR)	Pamelor and others
Nusinersen (PR)	Spinraza
Ofloxacin (PR)	Floxin
Olanzapine (CR)	Zyprexa and others
Oliceridine (PR)	Olinvyk
Omeprazole (CR)	Losec and others
Ondansetron (KR)	Zofran and others
Osilodrostat (PR)	Isturisa
Osimertinib (PR)	Tagrisso
Oxaliplatin (KR)	Eloxatin
Oxytocin (PR)	Pitocin and others
Ozanimod (PR)	Zeposia
Paliperidone (PR)	Invega and others
Palonosetron (PR)	Aloxi
Panobinostat (PR)	Farydak
Pantoprazole (CR)	Protonix and others
Papaverine HCl (Intra-coronary) (KR)	
Paroxetine (CR)	Paxil and others
Pasireotide (PR)	Signifor
Pazopanib (PR)	Votrient
Pentamidine (KR)	Pentam
Perflutren lipid microspheres (PR)	Definity and others
Perphenazine (PR)	Trilafon and others
Pilsicainide (PR)	Sunrythm
Pimavanserin (PR)	Nuplazid

Generic Name	Brand Name
Pimozide (KR)	Orap
Pipamperone (PR)	Dipiperon and others
Piperacillin/Tazobactam (CR)	Tazosyn and others
Pitolisant (Tiprolisant) (PR)	Wakix
Posaconazole (CR)	Noxafil and others
Pretomanid (PR)	
Primaquine phosphate (PR)	
Probucol (KR)	Lorelco
Procainamide (KR)	Pronestyl and others
Promethazine (PR)	Phenergan
Propafenone (CR)	Rythmol SR and others
Propofol (KR)	Diprivan and others
Prothipendyl (PR)	Dominal and others
Quetiapine (CR)	Seroquel
Quinidine (KR)	Quinaglute and others
Quinine sulfate (CR)	Qualaquin and others
Ranolazine (CR)	Ranexa and others
Remimazolam (PR)	Byfavo
Ribociclib (PR)	Kisqali
Rilpivirine (PR)	Edurant and others
Risperidone (CR)	Risperdal
Romidepsin (PR)	Istodax
Roxithromycin (KR)	Rulide and others
Rucaparib (PR)	Rubraca
Saquinavir (PR)	Invirase(combo)
Selpercatinib (PR)	Retevmo
Sertindole (PR)	Serdolect and others
Sertraline (CR)	Zoloft and others
Sevoflurane (KR)	Ultane and others
Siponimod (PR)	Mayzent
Solifenacin (CR)	Vesicare
Sorafenib (PR)	Nexavar
Sotalol (KR)	Betapace and others
Sparfloxacin (KR)	Zagam

Generic Name	Brand Name
Sulpiride (KR)	Dogmatil and others
Sultopride (KR)	Barnetil and others
Sunitinib (PR)	Sutent
Tacrolimus (PR)	Prograf and others
Tamoxifen (PR)	Nolvadex and others
Tazemetostat (PR)	Tazverik
Telaprevir (CR)	Incivo and others
Telavancin (PR)	Vibativ
Telithromycin (PR)	Ketek
Terfenadine (KR)	Seldane
Terlipressin (KR)	Teripress and others
Terodiline (KR)	Micturin and others
Tetrabenazine (PR)	Nitoman and others
Thioridazine (KR)	Mellaril and others
Tiapride (PR)	Tiapridal and others
Tipiracil/Trifluridine (PR)	Lonsurf
Tizanidine (PR)	Zanaflex and others
Tolterodine (PR)	Detrol and others
Toremifene (PR)	Fareston
Torsemide (Torasemide) (CR)	Demadex and others
Tramadol (PR)	Crispin and others
Trazodone (CR)	Desyrel and others
Trimipramine (PR)	Surmontil and others
Tropisetron (PR)	Navoban and others
Valbenazine (PR)	Ingrezza
Vandetanib (KR)	Caprelsa
Vardenafil (PR)	Levitra
Vemurafenib (PR)	Zelboraf
Venlafaxine (PR)	Effexor and others
Voriconazole (CR)	VFend
Vorinostat (PR)	Zolinza
Ziprasidone (CR)	Geodon and others
Zotepine (PR)	Losizopilon and others
Zuclopenthixol (Zuclopentixol) (PR)	Cisordinol and others

Note: [illegible] ongoing basis to assure [illegible] available evidence [illegible] continued placement on [illegible] because, the list is [illegible] ly, we re[illegible]org for the m[illegible]ple brand nam[illegible]he CredibleMeds website provides a partial list of the more common brands.

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