20 November 2014
EMA/CHMP/476353/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Otezla

International non-proprietary name: apremilast

Procedure No. EMEA/H/C/003746

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Otezla
Applicant:	Celgene Europe Limited 1 Longwalk Road Stockley Park UxbridgeUB11 1DB United Kingdom
Active substance:	apremilast
International Nonproprietary Name/Common Name:	apremilast
Pharmaco-therapeutic group (ATC Code):	Immunosuppressant (L04AA32)
Therapeutic indications:	<u>Psoriatic arthritis</u> 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). <u>Psoriasis</u> 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).
Pharmaceutical form:	Film-coated tablet
Strengths:	10 mg, 20 mg and 30 mg
Route of administration:	Oral use
Packaging:	Blister (PVC/aluminium foil)

Package sizes:	4 x 10 mg + 4 x 20 mg + 19 x 30 mg tablets 56 x 30 mg tablets and 168 x 30 mg tablets

Table of contents

List of abbreviations

AAR	Apremilast Subjects as Randomized/Re-randomized
AAT	Apremilast Subjects as Treated
ACR 20/50/70	20%/50%/70% improvement per the American College of Rheumatology response criteria
ACR-N	American College of Rheumatology N index
APR 20 BID / APR 30 BID	Treatment group comprising subjects initially randomized to apremilast 20 or 30 mg BID
APR 20 BID EE / APR 30 BID EE	Treatment group comprising subjects in the APR 20 BID / APR 30 BID treatment groups who entered early escape at Week 16
APR 20 BID NEE / APR 30 BID NEE	Treatment group comprising subjects in the APR 20 BID / APR 30 BID treatment groups who did not enter early escape at Week 16
APR	Apremilast
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BID	Twice daily
BOCF	Baseline observation carried forward
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
CASPAR	Classification Criteria for Psoriatic Arthritis
CDAI	Clinical Disease Activity Index
DAS28(CRP) 28	Joint Disease Activity Score using CRP as acute phase reactant
DIP	Distal interphalangeal
DMARD	Disease-modifying antirheumatic drug
DSC	Differential scanning calorimetry
DVS	Dynamic vapor sorption
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Subscale
FAS	Full analysis set
FT-IR	Fourier Transform InfraRed
GC	Gas chromatography

GRAPPA	Group of Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire – Disability Index
HPLC	High-performance liquid chromatography
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
LOCF	Last observation carried forward
LS	Least-squares
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	Minimal clinically important difference
MCS	Mental component summary(SF-36v2)
MMRM	Mixed-effects model for repeat measures
MTX	Methotrexate
NMR	Nuclear magnetic resonance
NRI	Nonresponder imputation
NSAID	Nonsteroidal anti-inflammatory drug
PASI	Psoriasis area and severity index
PASI-50	50% or greater improvement in Psoriasis Area and Severity Index score
PASI-75	75% or greater improvement in Psoriasis Area and Severity Index score
PBO/20 EE / PBO/30 EE	Treatment group comprising subjects initially randomized to placebo who entered early escape and were re-randomized to apremilast 20 or 30 mg BID at Week 16
PBO/20 XO / PBO/30 XO	Treatment group comprising subjects initially randomized to placebo who were re-randomized to apremilast 20 or 30 mg BID at Week 24
PCS	Physical component summary
PD	Pharmacodynamic
PDE4	Phosphodiesterase 4
PGA	Patient's (Subject's) Global Assessment
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)

PP	Per protocol
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PVC	Polyvinyl chloride
RH	Relative humidity
SCQ	Sponsor created queries
SF-36v2	The Short Form (36) Health Survey
SMQ	Standardised MedDRA Queries
TGA	Thermal gravimetric analysis
UPLC	Ultra Performance Liquid Chromatography
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celgene Europe Limited submitted on 2 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Otezla, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 March 2013.

The applicant applied for the following indication:

"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, or who have a contraindication to a DMARD therapy. Otezla has been shown to improve physical function.

Psoriasis:
Otezla is indicated for the treatment of adult patients with moderate to severe plaque psoriasis (PSOR) who are candidates for phototherapy or systemic therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that apremilast was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0171/2012 and P/0139/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIPs P/0171/2012 and P/0139/2013 were not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance apremilast contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 June 2010. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Otezla has been given a Marketing Authorisation in the US on 21 March 2014 for the treatment of adults with active psoriatic arthritis (PsA) and on 23 September 2014 for the treatment of psoriasis. Otezla has been given Marketing Authorisation in the Canada on 12 November 2014 for the treatment of psoriasis.

A new application was filed in the following countries: Australia, Switzerland and Israel.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturer

Manufacturer responsible for batch release

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
Middlesex
UB11 1DB
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Salmon Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 2 December 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2014.
- During the meeting on 10 April 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 02 September 2014.
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 October 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding issues to all CHMP members on 28 October 2014.
- During the meeting on 6 November the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During a meeting of the Safety Working Party (SWP) on 28 October 2014, experts were convened to address questions raised by the CHMP.
- During the meeting on 20 November 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing

Authorisation to Otezla.

2. Scientific discussion

2.1. Introduction

Problem statement

Psoriatic arthritis is a chronic inflammatory disease which may lead to progressive joint inflammation and injury, impaired functional activity and reduced quality of life, necessitating chronic, continual treatment to ensure disease control (Gladman, 2001; Mease, 2005a). Current therapies do not always adequately control the disease in all patients. Ultimately, most therapies fail to maintain clinical disease control over time. An unmet medical need for new treatments remains high, especially for therapies that confer a favorable benefit/risk profile, have alternative mechanisms of action, are convenient to use, and address both the rheumatic and dermatologic manifestations of PsA.

Psoriasis is a chronic disease that requires long-term treatment, ideally with effective agents that offer convenient dosing and a favorable benefit/risk profile. Despite the variety of treatment options available, patients are often dissatisfied with current therapeutic approaches, and their compliance with treatment is poor. Given the limitations associated with current therapies for moderate to severe plaque psoriasis, there remains an unmet medical need for an effective treatment, along with a low incidence and severity of adverse events that offers convenient oral dosing.

About the product

Apremilast (CC-10004) is a novel, oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) that works intracellularly to modulate a network of pro- and anti-inflammatory mediators.Phosphodiesterase 4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and is the dominant PDE in inflammatory cells. Inhibition of PDE4 elevates intracellular cAMP levels, which in turn downregulates the inflammatory response by modulating the expression of tumor necrosis factor alpha (TNF-α), interleukin (IL)-23, IL-17, and other proinflammatory cytokines. Elevation of cAMP also increases anti-inflammatory cytokines. These pro- and anti-inflammatory mediators have been implicated in psoriasis and psoriatic arthritis (PsA) (Schafer, 2010). The proinflammatory mediators that are upregulated in PsA include the cytokines TNF-α, IL-1,IL-6, and IL-8, and the chemokines monocyte chemotactic protein-1 (MCP-1) and macrophageinflammatory protein-1 beta (MIP-1β) (CC-10004-PSA-002-PD).

Based on these effects, apremilast is being developed for use in the treatment of various immune-mediated inflammatory conditions such as psoriasis, PsA, rheumatoid arthritis (RA), Behçet disease (BD), and ankylosing spondylitis (AS). A total of 4089 subjects have been exposed to apremilast across multiple indications, including 1945 subjects in the PsA Phase 3 clinical program and 1184 subjects in the PSOR Phase 3 clinical program.

The proposed therapeutic indication is:

"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, or who have a contraindication to a DMARD therapy. Otezla has been shown to improve physical function.

Psoriasis

"Otezla is indicated for the treatment of adult patients with moderate to severe plaque psoriasis (PSOR) who are candidates for phototherapy or systemic therapy."

Type of application and aspect on development

The applicant has undertaken a comprehensive clinical development programme covering the essential aspects in relation to this new chemical entity within the Phase I Clinical Pharmacology and Phase2/3 Efficacy and Safety programmes. In addition to standard pharmacokinetics and pharmacodynamics, the package incorporates PK/PD modelling aspects across the development programme which provides a thorough understanding of the handling and behaviour of apremilast within the target patient population and special groups who might receive this treatment. The data submitted also address the other aspects of the product specifications including potential interactions and adverse drug reactions. The development programme, as well as complying with the relevant EU Guidelines for the two proposed indications (Guideline on clinical investigation of medicinal products for the treatment of psoriasis (CHMP/EWP/2454/02;2005) and psoriatic arthritis (CHMP/EWP/438/04; 2007), has taken into account regulatory precedence and the previous CHMP advice received on 24 June 2010 as summarised below:

Summary of CHMP Advice in each Indication

Psoriasis	**Psoriatic Arthritis (PsA)**
Conduct a membrane transporter study and a ciclosporin (CsA) drug interaction study to complement the submission package	
Use of PASI and PGA as endpoints.	Evaluation of two doses (20mg and 30mg) in pivotal studies
Use of Week 16 as an adequate time point for assessment of PASI-75 as a primary Endpoint.	Inclusion based on the Classification Criteria for Psoriatic Arthritis (CASPAR) and Functional Class I-III (ACR classification of Functional Status)
Use of Week 16 as an adequate time point for assessment of PASI-75 as a primary Endpoint.	Primary endpoint: modified ACR 20 response at week 24
Sensitivity analysis to support the use of the last observation carried forward (LOCF)	Proposed statistical methodology including sample size and use of non-responder imputation (NRI) for subjects who discontinue early or meet the early escape (EE) criteria at week 16.
Placebo-controlled design acceptable (inclusion of an active comparator arm in one of the pivotal studies is recommended) (see below)	Placebo-controlled design. Inclusion of an active comparator in at least one Phase 3 study useful but not mandatory.

Withdrawal design and time points acceptable, definition of loss of response to be Reconsidered.	52 weeks' efficacy data showing maintenance of effect.
Stratification to previous therapies, history of psoriasis, background treatment Standardisation.	
Long-term data (52 weeks) for submission.	The pivotal studies would only support a second-line indication (after inadequate response to DMARDs)

The applicant considered that all key points from the Scientific Advice received have been addressed in the design of the clinical studies, with the exception of the following points for which a justification for deviation has been provided:

- **Psoriasis (PSOR) programme**
  - CsA interaction study: This has been omitted as justified by the applicant in section 2.1.10.
  - *Stratification:* Although the Phase 3 trials were not stratified according to previous therapies, history of PSOR, and background treatment(s), these factors were generally well balanced between treatment groups and across studies.
  - Active comparator: after due consideration, the applicant's approach has been to use the limited patient resources available to fully characterise the efficacy and safety of APR in patients with moderate to severe plaque PSOR rather than include an active comparator arm. The applicant believes that etanercept is the most appropriate benchmark comparator and that its efficacy and safety profile has been well characterised in the target patient population. A comparison of the activity of APR with historic etanercept data is therefore considered by the Applicant to be feasible and to provide relevant information regarding the relative benefit/risk profile of APR.
- **Psoriatic Arthritis (PsA) programme**
  - Primary endpoint (modified ACR 20 response) – instead of being at Week 24 this was changed to Week 16 prior to database lock and unblinding. The Applicant decided to do this because, given the design of the study, Week 16 provided the only true placebo-controlled evaluation of the efficacy of APR, due to the early escape provision at this time-point for placebo-treated patients. The fact that recent clinical trials evaluating other systemic therapies in PsA have used primary endpoints between Weeks 12 to 16 supports the validity of this change (Antoni, 2005; Mease, 2005b; Kavanaugh, 2009).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablet containing 10 mg, 20 mg or 30 mg of apremilast as active substance.

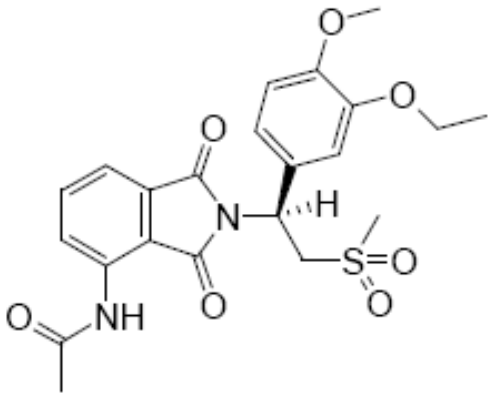
Other ingredients are: for the tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose calcium, magnesium stearate, for the film-coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide red (E172). The 20 mg tablets also contain iron oxide yellow (E172). The 30 mg tablets also contain iron oxide yellow (E172) and iron oxide black (E172).

The product is available in PVC/ aluminium foil blisters.

2.2.2. Active Substance

General information

The chemical name of apremilast is N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide and has the following structure:



Apremilast is a white to pale-yellow non hygroscopic powder, practically insoluble in aqueous buffers irrespective of pH range, soluble in acetone, acetonitrile, methylethylketone, methylene chloride and tetrahydrofuran. Active substance is classified as having low solubility and low permeability according to Biopharmaceutical Classification System (i.e. BCS Class 4).

The chemical structure of apremilast has been adequately demonstrated by elemental analysis, IR and UV spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, single crystal X-ray diffraction and XRPD, DSC, TGA, DVS and particle size distribution, and a polymorphism screen (polymorphs were characterised using XRPD, DSC, TGA, DVS, TGA/FT-IR and microscopic examination).

Apremilast exhibits stereoisomerism due to presence of a single chiral centre, with the (S)-enantiomer being pharmacologically active. Active substance stability studies and clinical studies have demonstrated that there is no interconversion of apremilast (S)-enantiomer to its (R)-enantiomer both on storage and

in vivo. Polymorphism has been observed for apremilast and seven polymorphic forms (designated A-G) of the active substance were identified. The desired form B was found to be the most thermodynamically stable anhydrous form of apremilast. The manufacturing process consistently yields active substance of single crystal form B.

Manufacture, characterisation and process controls

Apremilast active substance is obtained from two manufacturers.

The synthesis of apremilast is well described. Two manufacturing processes have been proposed for the synthesis of the active substance. Both processes use the same synthetic route, but differ primarily in the solvents that are used in the isolation of crude active substance.

The designation of starting materials was revised during the assessment procedure.

Apremilast is synthesized in either 4 main steps or 3 main steps, using commercially available, well defined starting materials with acceptable specifications. The proposed manufacturing processes differ in the initial stages of synthesis with different isolated intermediates in which chiral purity is controlled. The manufacture of apremilast active substance includes the following steps common to both processes: i) coupling (chemical transformation) of the starting materials and intermediates to yield apremilast crude and ii) recrystallisation and drying of apremilast crude to yield the desired polymorph, Form B. The synthetic route used in the manufacturing process of the active substance is designed to manufacture (S)-enantiomer (i.e. pharmacologically active moiety), with enantiomeric purity routinely controlled by chiral HPLC. It was demonstrated that there is no inter-conversion between the two enantiomers during the manufacturing process and that the final level of the (R)-enantiomer in the active substance reflects that present in the intermediates.

Manufacturing process validation has been carried out for both processes on each of the manufacturing sites.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on Chemistry of New Active Substances. Potential and actual impurities were well discussed with regards to their origin and characterisation.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for: appearance (visual examination), identity (FT-IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), chiral purity (HPLC), heavy metals (Ph. Eur.), residue on ignition (Ph. Eur.), and particle size (laser diffraction).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data (n=47, 19 of which are commercial scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches of active substance, stored in a container closure system representative of that intended for the market for 36 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines, were provided.

Additionally, stability data on one commercial scale batch of active substance, stored in a container closure system representative of that intended for the market for 24 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines, was provided.

Finally, stability data on three commercial scale batches of active substance, stored in a container closure system representative of that intended for the market for up to 18 months, under long term conditions at 25 ºC / 60% RH according to the ICH guidelines, were provided.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions under acid, base, oxidation and thermal stress were also provided on one batch.

The following parameters were tested*:* appearance, assay and impurities, water, chiral purity and polymorphic form. The parameters include those tested for release, with some additional parameters being monitored. The analytical methods used were the same as for release and are stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the pharmaceutical development was to develop an immediate release solid dosage form for oral use providing high bioavailability of the active substance that is practically insoluble in water (7 µg/mL at room temperature). In order to allow for flexibility in posology requirements, film-coated tablets containing 10 mg, 20 mg or 30 mg of apremilast as active substance were developed.

Physico chemical properties of active substance that could affect critical quality attributes (assay, content uniformity, and dissolution), were assessed. During formulation development, different formulations were developed. The proposed commercial formulation contains qualitatively the same core formulation composition as the formulation used in phase III clinical studies. These formulations were manufactured by the essentially the same manufacturing process. Changes in formulation have been supported by dissolution studies and f_2 comparisons showing adequate product development. In particular dissolution comparison was carried out at three pH values, between formulation tablets used in clinical studies and commercial formulation tablets. Certain bioequivalence and bioavailability data in support of formulations during development has been provided.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except the proprietary Opadry II coating material. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Compatibility studies of apremilast with all excipients used in the proposed commercial formulation were conducted and compatibility was demonstrated.

Pharmaceutical development of the finished product contains QbD elements. Firstly the applicant carried out risk assessments to identify medium to high risk material attributes and process variables and to determine which studies were necessary to achieve product and process understanding in order to develop a control strategy. Quality by Design (QbD) studies were then conducted using a Design of Experiments (DoE) approach in order to characterise the impact of the medium to high risk parameters on the Critical Quality Attributes (CQA) of the finished product. Quality target product profile (QTPP) was established and it is analogous to the finished product specifications.

The quality target product profile (QTPP) was defined as an immediate release dosage form suitable for oral route of administration that meets compendial and other relevant quality standards, and maintains the required quality attributes throughout shelf life.

The critical quality attributes identified were assay, content uniformity and dissolution. Appearance was a CQA in coating process.

The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. The risk identification was based on the experience from formulation development, process design and DoE studies. The critical process parameters have been adequately identified.

Extensive knowledge of the product has been gained by this development approach, however it is not proposed to apply a design space as the relevant parameters impacting finished product performance are controlled using a control strategy which includes control of material attributes, control of critical process parameters and finished product specifications. The dissolution method was developed considering the physico chemical characteristics of the active substance and the finished product. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is PVC/ aluminium foil blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of three main steps: i) blending and lubrication process, ii) compression process and iii) coating process. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for standard manufacturing process of film-coated tablets.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (UV, UPLC), assay (UPLC), degradation products (UPLC), content uniformity/ uniformity of dosage units (UPLC), dissolution (UPLC), and microbial limits (Ph. Eur.). The suitability of the methods in control of the finished product was demonstrated.

Batch analysis results are provided for 28 batches, 25 of which were commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 4 pilot scale batches of each strength for up to 24 months and 16 commercial scale batches of 10 mg and 20 mg strength, as well as 17 commercial scale batches of 30 mg strength of finished product stored under long term conditions for up to 18 months at 30 ºC / 60% RH and data of 4 pilot scale batches of each strength and 16 commercial scale batches of 10 mg and 20 mg strength, as well as 17 commercial scale batches of 30 mg strength of finished product for up to 9 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay (UPLC), degradation products (UPLC), dissolution (UPLC), and microbial limits (Ph. Eur.). The analytical procedures used are stability indicating.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Based on observed variability of batch analysis data for dissolution under accelerated conditions, a storage condition of 'do not store above 30 °C' was implemented.

Based on available stability data, the shelf-life as stated in the SmPC is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical pharmacology programme for Otezla consisted of pharmacodynamic studies in in vitro assays and in vivo animal models of inflammatory conditions, and safety pharmacology studies. Pharmacokinetic studies were performed to determine ADME and drug-drug interaction potential. The nonclinical toxicology programme included single-dose toxicity studies in mice and rats, a series of repeat-dose toxicity studies for dosing durations up to 6 months in mice and 12 months in monkeys, genotoxicity core battery studies, carcinogenicity studies in mice and rats including 3-month maximum tolerated dose (MTD) studies to select the dosages for 2-year carcinogenicity studies, reproductive and developmental toxicity studies in mice and monkeys, local tolerance studies, and a juvenile mouse study.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In Vitro Pharmacodynamic Activity of Apremilast

Enzyme assays

The PDE4 enzyme assay results indicated that apremilast is a potent and selective inhibitor of the PDE4 enzyme isolated from U937 human monocytic cells (Muller, 1998) (half maximal inhibitory concentration [IC50] = 74 nM). The specificity of apremilast for PDE4 inhibition was assessed by testing a single concentration (10 µM) against PDE1, PDE2, PDE3, PDE5, PDE6, PDE7, and PDE11 enzymes. The results indicated that apremilast was between approximately 279- to 40,000-fold more selective for PDE4 inhibition compared with the other PDE enzymes.

Apremilast was also investigated for PDE enzyme specificity and was tested against additional recombinant human PDEs 1A, 1C, 2A, 3A, 3B, 4A1A, 4B1, 4B2, 4C1, 4D2, 5A1, 7A, 7B, 8A1, 9A2, 10A1, and 11A4 at room temperature for 1 hour. Apremilast displayed an average of ≈ 95% (range: 91% to 99%) inhibition of the PDE4 enzymes (A1A, B1, B2, C1, and D2) in a largely non-selective manner, without significant inhibition of other PDEs tested. In dose response inhibition assays (0.001 µM - 10 µM apremilast) on recombinant human PDE4s A1A, B1, B2, C1, D2, D3, and D7, IC_{50} values were 14, 43, 27, 118, 33, 28, and 30 nM, respectively.

Apremilast also binds to the high affinity rolipram binding site (HARBS) form of the PDE4 enzyme from rat brain. Binding of a PDE4 inhibitor to HARBS has been correlated with increased acid production in rabbit gastric acid glands (Barnette, 1995). Also apremilast (IC50 = 74 nM), an optically pure S-isomer of the racemate CC-7085, was 8-fold more potent than its R-isomer CC-10007 (IC50 = 611 nM) for PDE4 enzyme inhibition. Since apremilast does not interconvert to the R-isomer in animals or humans, none of the pharmacological activity of apremilast is derived from the R-isomer.

Binding specificity was investigated in non-GLP study. Apremilast (10 µM) was profiled for binding to 68 cell surface receptors and for inhibition of 17 enzymes (Report 8611). The results demonstrated that apremilast had no significant activity against any of the receptors or enzymes, except for 95% inhibition of PDE4, and 52% enhanced agonist binding of the L-type (verapamil) calcium channel receptor. However, results from a subsequent study (Report CC-10004-ET-151) confirmed that the 52% inhibition of the L-type (verapamil) calcium channel observed at 10 µM apremilast was a false positive hit. Kinase

inhibition profiling of apremilast (10 µM) using Invitrogen's SelectScreen® Profiling Service demonstrated that the compound did not significantly inhibit any of the 255 kinases tested.

Cellular Assays of Inflammatory Responses

Apremilast was evaluated in human cellular assays examining effects on cytokines derived from monocytes and T cells, PGE2 production, cAMP elevation, cyclooxygenase (COX)-2 expression, neutrophil adhesion, endothelial cell migration, and antiproliferative/antiangiogenic activity (Table 1) (Report 5042-107; Report 5424-11; Report 5478-159; Report 5299-148; Report 5197-130; Report 5279-153; Report 5127-132; Report 5478-100; Report 5638-35).

Table 1: Cellular Pharmacologic activity of apremilast

Cellular Effects	**IC_{50} (nM)**	**IC_{50} (ng/mL)**
LPS-induced HPBMC TNF-α	77	35
LPS-induced human whole blood TNF-α	294	135
LPS-induced HPBMC IL-12	140	64
LPS-induced HPBMC IL-10	EC_{50} = 2300	EC_{50} = 1100
Human helper (CD4+) T cell IL-5	890	410
IL-1β induced HPBMC TNF-α	83	38
SEB-induced HPBMC IL-2	291	134
SEB-induced HPBMC IFN-γ	46	21
fMLF-induced neutrophil LTB4	2.50	1.20
fMLF-induced neutrophil CD18 expression	390	180
fMLF-induced neutrophil CD11b expression	74	34
fMLF-induced neutrophil HUVEC adhesion	150	69
Zymosan-induced neutrophil IL-8	94	43
TNF-α stimulated GM-CSF production in NHLFs	120	55
CpG-A ODN 2216 (1 µM) stimulation of hPBMCs IFN-α	620	286
CpG-A ODN 2216 (10 µM) stimulated human pDC IFN-α	480	221
CpG-A ODN 2216 (1 µM) stimulation of hPBMCs TNF-α	120	55
CpG-A ODN 2216 (10 µM) stimulation of human pDC TNF-α	270	124
Multiplex Cytokine Analysis from LPS-induced HPBMCs	**IC_{50} (nM)**	**IC_{50} (ng/mL)**
TNF-α production	110	51
IL-1β production	> 100,000	> 46,000
IL-8 production	> 100,000	> 46,000
IL-12 production	120	55
GM-CSF production	7800	3600
MIP-1α production	440	200
MCP-1 production	1300	600

Multiplex Cytokine Analysis from LPS-induced HPBMCs	IC_{50} (nM)	IC_{50} (ng/mL)
RANTES production	> 100,000	> 46,000
IL-6 (maximum increase of 100%)	EC_{50} = 11,000	EC_{50} = 5100
IL-10 (maximum increase = 50%)	EC_{50} = 80	EC_{50} = 37
Multiplex Cytokine Analysis from AntiCD3 mAb-stimulated Primary Human T cells	**IC_{50} (nM)**	**IC_{50} (ng/mL)**
IL-5 production	30	14
IL-17 production	90	41
IL-10 production	190	88
IL-13 production	280	130
TNF-α production	930	430
GM-CSF production	1000	470
Enzymatic and Cellular Inhibition	**IC_{50} (nM)**	**IC_{50} (ng/mL)**
IFN-γ production	1300	580
IL-2 production	2400	1100
RANTES production	4100	1900
cAMP and PGE_2 Elevation	**EC (nM)**	**EC (ng/mL)**
PGE_2-induced HPBMC cAMP EC_{50}	EC_{50} = 1510	EC_{50} = 695
PGE_2-induced neutrophil cAMP EC_{50}	EC_{50} = 4570	EC_{50} = 2100
PGE_2 elevation in LPS-induced HPBMCs	EC_{120} = 85	EC_{120} = 39
PGE_2 elevation in PHA-induced HPBMCs	EC_{200} = 85	EC_{200} = 39
Nitric Oxide and E-Selectin Expression	**% Inhibition at 10 µM**	
IL-1β-induced HUVEC nitric oxide	87%	
TNF-α-induced HUVEC E-Selectin expression	25% by PGE_2/apremilast combination	

cAMP = cyclic adenosine monophosphate; EC_{50} = effective concentration for 50% maximal response; $EC_{150\ (200)}$ = effective concentration for 1.5x (2x) normal response; fMLF = N-formyl-methionine-leucine-phenylalanine; GM-CSF = granulocyte macrophage-colony stimulating factor; HPBMC = peripheral blood mononuclear cell; HUVEC = human umbilical vein endothelial cell; IC_{50} = 50% inhibitory concentration; IFN-γ = interferon-gamma; IL = interleukin; LPS = lipopolysaccharide; LTB4 = leukotriene B4; mAb = monoclonal antibody; MCP-1 = monocyte chemotactic protein-1; MIP-1α = macrophage inflammatory protein-1α; NHLF = normal human lung fibroblast; PGE_2 = prostaglandin E_2; PHA = phytohemagglutinin; RANTES = regulated upon activation, normal T-cell expressed, and presumably secreted; SEB = staphylococcal enterotoxin B; TNF-α = tumor necrosis factor-alpha.

Human whole blood, pre-treated for 1 hour with apremilast (0.5 and 1.5 μM), was stimulated with LPS for 18 hours using a TruCulture™ System (Report 7600-043). Apremilast had significant inhibitory effects at 0.5 and 1.5 μM on TNF-α, IL-12/IL-23 p40, interferon gamma inducible protein 10 (IP-10), and MCP-1

production in LPS-stimulated human whole blood ($p < 0.001$). Apremilast also had significant inhibitory effects at 1.5 μM on IL-23 p19 and total IL-23 production ($p < 0.001$). There was no effect on IL-10 production in whole blood in this system. IFN-γ, IL-12 p70, IL-17A, and IL-22 were below the limit of quantitation. The inability to quantify IL-12p70 in this system suggested that the IL-12/IL-23 p40 expressed in this system is predominantly in complex with IL-23 p19.

Gene expression studies

To study the intracellular mechanism of action of apremilast on the PKA and NF-κB pathways, Jurkat T cells and THP-1 monocytic cells were incubated with apremilast (0.1 - 1 μM) alone, or with forskolin (10 μM each), for 30 minutes (Report 7600-011). Jurkat T cells and THP-1 monocytic cells were also incubated under the same conditions with IκB kinase (IKK) inhibitor VII for 1 hour, followed by stimulation with recombinant human TNF-α (rhTNF-α) or LPS, respectively, for an additional hour. Apremilast modulated pro- and anti-inflammatory gene expression by activating the PKA-CREB pathway, resulting in enhancement of cAMP responsive element (CRE)-driven gene transcription and inhibition of NF-κB-driven gene transcription. To study the effects of apremilast on gene expression, HPBMCs and monocytes were stimulated for 24 hours and 6 hours, respectively, after incubation with 1 μM apremilast for 1 hour. These gene expression studies in LPS-stimulated HPBMCs and monocytes identified several targets of gene regulation by apremilast, with effects including the inhibition of many chemokines, chemokine receptors, and Th1 cytokine genes, as well as enhancement of the genes encoding the anti-inflammatory factor suppressor of cytokine signalling 3 (SOCS3), the chemokine epithelial-derived neutrophilactivating peptide 78 (ENA-78), and growth factors amphiregulin and bone morphogenic protein 6 (BMP-6).

Apremilast inhibited protein expression of IFN-γ, IP-10, MIG, and TNF-α, but enhanced MMP-1 expression (EC_{50} = 0.017 μM). However, the effect on MMP-1 was biphasic, enhancing production at 0.1 and 1 μM but inhibiting at 10 μM (Report 5478-100; Report BSK-1073). After 6 hours of incubation with 1 μM apremilast in LPS-stimulated human monocytes, there was a 1.53-fold increase in IL-10 gene expression; however, the change was not statistically significant (Report 7600-011).

The T cell regulatory cytokine IL-7, produced by chondrocytes and synoviocytes, plays a role in inflammatory joint diseases such as arthritis and in bone damage (Long, 2008). In particular, IL-7 mRNA and protein levels were increased in synovial fluid of spondylarthritis and RA patients (Rihl, 2008). In normal primary human, chondrocytes stimulated with IL-1, IL-6, and IL-6 receptor (IL-6R) for 18 hours, apremilast (0.1 - 10 μM) significantly inhibited IL-7 gene expression in a dose-dependent manner (Report 5673-140). In this assay, apremilast was a more effective inhibitor of IL-7 gene expression than methotrexate (MTX) and ETAN within dose ranges that encompassed their respective maximum plasma concentrations (C_{max}: MTX = 400 ng/mL and ETAN = 1600 ng/mL). Conversely, apremilast was not as effective as prednisolone (PRED). Also, in stimulated primary human normal chondrocytes, apremilast weakly inhibited expression of the synovial tissue biomarkers ICAM-1 and alpha-v-beta-3 (αvβ3) integrin. In rheumatoid arthritis (RA) synovial fibroblasts stimulated with IL-1, IL-6, and IL-6R, apremilast significantly inhibited IL-7 gene expression in a dose-dependent manner.

PDE4 inhibitors have been shown to elevate PGE2 production by HPBMCs (Banner, 1999), an effect that may involve the activation of a cAMP responsive element in the COX-2 promoter (Schroer, 2002). The effect of apremilast (up to 100 μM) on COX-2 expression and subsequent PGE2 formation by HPBMCs was therefore examined (Report 5197-130). Apremilast, added 1 hour prior to 20 hours of stimulation, increased COX-2 and PGE2 production by LPS- or phytohemagglutinin (PHA)-stimulated HPBMCs by 50% to 100%, demonstrating that apremilast enhanced, rather than inhibited, COX-2 expression in stimulated HPBMCs. However, apremilast (up to 100 μM), added to human umbilical vein endothelial cells (HUVECs) or platelets 1 hour prior to the 18-hour incubation with platelets or calcium ionophore A23187,

respectively, did not affect either prostacyclin or thromboxane production in the HUVEC/platelet co-culture system, or in calcium ionophore-stimulated platelets, indicating that apremilast does not modulate the eicosanoid production pathway in these cell types (Report 5299-148).

Bone marrow mononuclear cells and normal human osteoblasts were incubated with apremilast at clinically relevant concentrations (0.1 - 1 μM) for 7 days (Report 7645-001). Apremilast significantly inhibited osteoclastogenesis at these concentrations. This effect was associated with a decrease in form of soluble receptor activator nuclear factor κ-B ligand (sRANKL) protein expression and an increase in BMP-6 gene expression in the osteoclast cultures, an effect which was also observed in osteoblast cultures. Apremilast decreased the sRANKL/osteoprotegerin (OPG) protein ratio in both osteoclast and osteoblast cultures, and the effect was more pronounced in the osteoblasts. In contrast, positive controls rolipram, alendronate, and sulphasalazine had no effect on the sRANKL/OPG protein ratio, indicating that apremilast acts by a distinct mechanism.

Comparative studies with other PDE4 inhibitors

The activity of PDE4 inhibitors apremilast, cilomilast, and roflumilast was compared using rat, mouse, monkey, and human whole blood stimulated with LPS in vitro (Report 5265-117). After one hour of LPS stimulation, these inhibitors caused a dose-dependent elevation in IL-6 production from LPS-stimulated whole blood from mouse (3- to 5-fold) and rat (2- to 3-fold), but not from monkey or human whole blood. Apremilast, cilomilast, and roflumilast essentially had no effect on human IL-6 production, and partially inhibited monkey IL-6 production (maximum of 50%). In conclusion, the PDE4 inhibitors apremilast, cilomilast, and roflumilast had a qualitatively different effect on LPS-induced IL-6 production in vitro by the whole blood of rodents compared to that of primates and humans. These results indicate that rodents are more sensitive to PDE inhibitor-induced inflammatory response than primates and humans.

Evaluation of antiproliferative effects

Normal human lung fibroblast (NHLF) were incubated with apremilast (0.0001 - 100 μM) for 1 hour prior to the addition of LPS (1 ng/mL), TNF-α (10 ng/mL), or transforming growth factor-β 1 (TGF-β 1) (10 ng/mL) for 24 or 48 hours, followed by ^{3}H-thymidine incorporation for 24 or 48 hours (Report 5299-083). Apremilast displayed weak antiproliferative effects on NHLF in the 24-hour ^{3}H-thymidine assay (IC_{50} values >100 μM under LPS, TNF-α, or TGF-β1 stimulated conditions). The apremilast antiproliferative activity improved in the 48-hour assay with IC_{50} values of 92, 40 and 52 μM for the LPS, TNF-α, and TGF-β1 conditions, respectively.

Human dermal fibroblasts (HDFs) were treated for 1 hour with apremilast (0.00001 - 10 μM), followed by incubation with IL-1β (1 ng/mL), TNF-α (5 ng/mL), or IFN-γ (20 ng/mL) for 72 hours and then ^{3}H-thymidine incorporation for 6 hours (Report 5570-044). After HDFs were stimulated, apremilast displayed no observable antiproliferative effect on HDF survival in the concentration range tested (IC_{50} > 10 μM). The effect appeared to be biphasic, with 30% enhancement at 0.1 μM but with proliferation returning to baseline at 10 μM.

Plasminogen activator inhibitor-1 (PAI-1) is associated with fibroblast proliferation. In order to determine the effects of apremilast on PAI-1 production, HDFs were treated for 1 hour with apremilast (0.00001 - 10 μM), followed by stimulation with rhIL-1β (1 ng/mL), rhTNF-α (5 ng/mL), or rhIFN-γ (20 ng/mL) for 24 hours (Report 5570-044). Results from a human PAI-1 ELISA indicated that 10 μM apremilast displayed weak PAI-1 inhibitory effects achieving approximately 17% inhibition. However, at approximately 0.1 μM apremilast, the effect on PAI-1 expression and fibroblast proliferation started to decline (Report BSK-1073).

Evaluation of antiangiogenic potential

The effect of apremilast on VEGF-induced HUVEC proliferation and intracellular signalling was examined (Report 5279-153). After 1-hour incubation with apremilast (0.001 - 100 μM), followed by stimulation with VEGF or basic fibroblast growth factor (bFGF) for 72 hours, apremilast inhibited VEGF-induced HUVEC proliferation in a concentration-dependent manner with an IC_{50} value of 6.7 μM, but was an ineffective inhibitor in the bFGF-induced proliferation assay. Also, apremilast (100 μM) displayed a significant inhibitory effect on Ser473-Akt phosphorylation but failed to block Akt phosphorylation at the Thr308 site. In the human angiogenesis assay, apremilast inhibited sprout formation from human umbilical cord blood vessels in a concentration-dependent manner with an IC_{50} = 0.14 μM (Report 5127-132). Additionally, after 18 hours of LPS stimulation of HUVECs, apremilast (10 μM; 4.6 μg/mL) inhibited IL-1β-induced nitric oxide production by 87%, indicating a potential suppressive effect on nitric oxide synthase isozyme expression in endothelial cells (Report 5042-107). These results indicated that apremilast inhibits VEGF signalling and new blood vessel formation via endothelial cells, and block endothelial cell proliferation, and therefore may have an impact on angiogenic processes such as those that occur in PsA and PSOR (Coates, 2008b).

The effect of apremilast on hypoxia-inducible factor (HIF)-1α and p53 tumor suppressor protein expression in HUVECs under hypoxic conditions was investigated (Report 5387-08). Time course results showed that HIF-1 α protein begins accumulating in approximately 30 minutes under hypoxic conditions, with maximum accumulation between 120 - 240 minutes. In HUVECs, apremilast inhibited the VEGF-induced VEGF receptor tyrosine phosphorylation (100 μM) and mitogen-activated protein kinase (MAPK) phosphorylation. Also, apremilast (0.01 - 10 μM) inhibited HIF-1α protein expression in HUVECs under hypoxic conditions at 30 minutes and 2 hours within a range of 45% to 92%. Conversely, apremilast (0.1 - 10 μM) enhanced the p53 tumor suppressor protein expression ≈ 4-to 4.5-fold at the 18-hour time point, which diminished slightly at the 36-hour time point to yield a 2.3- to 2.9-fold enhancement, suggesting that apremilast enhances p53 tumor suppressor protein expression for up to 36 hours under hypoxic conditions. These findings illustrated the mechanism of apremilast antiangiogenic activity and its ability to enhance p53 tumor suppressor protein expression.

Pharmacological Activity of the Metabolic Products of Apremilast

In vivo, apremilast is converted to several metabolic products, including the hydrolysis degradants M1 and M2, the O-desmethyl metabolite M3 (tested as racemate CC-15604 and S-isomer CC-16085, respectively), the O-desethyl metabolite M5, the N-deacetyl metabolite M7, the O-desmethyl glucuronide metabolite M12, the N-deacetyl O-desmethyl glucuronide metabolite M14, the acetamide-hydroxy-glucuronide M16 and the acetamide-hydroxy metabolite M17. The synthesized metabolites, including M12 isolated from human urine, were assayed for PDE4 enzyme activity and TNF-α production, and compared with the parent drug (Report 5275-179, Report 5347-137, Report 5424-75; Report 5638-96). Only the M7 and M17 metabolites (represented as CC-10055 and CC-16401, respectively), demonstrated potent inhibition of both PDE4 enzyme activity and TNF-α production, indicative of pharmacologically active apremilast metabolites (Report 5275-179; Report 5424-75), albeit less potent than apremilast. These data showed that the major circulating and excreted metabolites of apremilast are inactive or markedly less active towards the PDE4 enzyme and TNF- α production. The two pharmacologically active metabolites M7 and M17, account for less than 1% of the apremilast plasma exposure, and are not anticipated to contribute to the pharmacodynamics effects to a notable extent (Report CC-10004-PK-002).

In Vivo Pharmacodynamic Activity of Apremilast

Apremilast pharmacology was investigated in *in vivo* animal models of disease, including inflammatory and arthritis rodent models, psoriasis mouse models, UVB-stimulated SKH-1 hairless mice, and T and B cell adaptive transfer models. Antiarthritic and anti-inflammatory activity of apremilast was investigated

in LPS, carrageen, and collagen-induced models of disease in rodents. Psoriasis effects were determined in the human skin xenograft model in mice. The studies and the relevant findings are summarised in Table 2:

Table 2: In vivo pharmacodynamic activity of apremilast

Study Number	Treatment Duration	Stimulus	Dose / Route of Administration	Study Type Species / Sex	Major Findings
Acute TNF-α Production, Inflammation, and Hyperalgesia					
5042-107	3.5 hours	LPS	0.01 - 1 mg/kg, PO	BALB/c mice Females	Apremilast inhibited LPS-induced serum TNF-α levels with an ED_{50} of 0.05 mg/kg.
AP279R, AP284R, AP291R	2.5 hours	LPS	0.01 - 10 mg/kg, PO	CD rats Females	Apremilast inhibited LPS- induced plasma TNF-α levels > 80% (ED_{50} = 0.018 mg/kg).
AP352R	5 hours	carragee-nan	10 mg/kg, PO	CD rats Females	Apremilast pretreatment reduced airpouch TNF-α levels by 82%, but neurotphil infiltration was unaffetcted.
1270RC35.001	3 days	carragee-nan	50 mg/kg (10mg/mL, IP)	Sprague- Dawley rats Males	Apremilast produced significant reductions in paw edema and biologically relevant increases in the 3-hour postdose threshold for both mechanical and thermal hyperalgesia at high dose.
AP343R	4 hours	carragee-nan	10 mg/kg, PO	CD rats Females	Apremilast had no effect on paw edema following carrageenan injection.
Collagen-induced Arthritis					
WEL 01-027	14 days (Days 21 to 34)	bovine type II collagen	1 or 10 mg/kg, PO, QD	DBA/1LacJ mice Females	In the collagen-induced arthritis model, apremilast inhibited paw edema by 49% at 1 mg/kg and 32% at 10 mg/kg.

AP707R, AP830R	17 days	bovine type II collagen and LPS	1, 5, and 25 mg/kg, PO, QD	DBA/1 LacJ mice Females	Apremilast significantly inhibited the paw score arthritis parameter on day 42 . However, a trend towards a decrease in arthritis severity was observed in Study AP830. Notably, the disease severity in the AP830 controls was lower than that in the AP707 controls.
KIR-P03604	10 days 48 hours	bovine type II collagen, LPS	5 or 25 mg/kg/day, IP	DBA/1Ola-Hsd mice	Apremilast was effective in reducing the clinical and histologic severity of arthritis in CIA mice at both doses. Apremilast did not produce the same behavioural changes elicited by the PDE4 inhibitor, rolipram
Collagen Antibody-induced Arthritis					
CLG/001/EM; CLG/001/EM-Histology	5 days	collagen mAB and LPS	1, 5, and 25 mg/kg, PO, QD	BALB/c mice Males	Apremilast, at 25 mg/kg for 5 days, demonstrated significant antiarthritic activity in the combined mAb cocktail and LPS-induced experimental arthritis mouse model. Apremilast treated mice had minimal histopathologic indications of arthritis. The antiarthritic activity of apremilast at 25 mg/kg was similar to dexamethasone at 1 mg/kg.

CLG/002/EM; CLG/002/EM-Histology	11 days	collagen mAB and LPS	5 or 25 mg/kg, PO, QD	BALB/c mice Males	Apremilast, at 5 and 25 mg/kg for 11 days, demonstrated significant antiarthritic activity in the combined mAb/LPS arthritis model. However, apremilast-treated mice had reduced histopathologic signs of arthritis, but these changes were not statistically significant. The antiarthritic activity of apremilast at 5 and 25 mg/kg, PO was similar to that of etanercept at 5 mg/kg, IP (8% to 28% reductions; Days 5 to 9).
CLG/003/EM; CLG003/EM-Histology	11 days	collagen mAb and LPS	5 mg/kg, PO, QD	BALB/c mice Males	Apremilast demonstrated significant antiarthritic activity in the mAb/LPS arthritis model. The histopathologic assessment did not validate the arthritis inhibition resulting from apremilast treatment due to the minimal-to-moderate arthritis disease level observed in control animals.
Xenograft-induced psoriasis					
TECH1102006	14 days	Human skin xenograft, psoriatic NK cells	5 mg/kg, PO divided BID	beige-SCID mice	Apremilast demonstrated reductions (≥ 50%) in both the epidermal thickness and keratinocyte proliferation index, psoriasiform histological features and immunohistochemical expression of the inflammatory markers TNF-α, HLA-DR and ICAM-1. Results were comparable to positive controls (cyclosporine).

UVB-induced apoptosis					
AP2599	Single dose	UVB	25 mg/kg PO	SKH-1 mice Female	Apremilast significantly decreased the number of TUNEL-positive cells measured 24 hours post UV exposure, indicating anti-apoptotic activity
5448-74	In vitro	UVB	0.1 – 10 µM		Apremilast displayed modest increases in cell cytotoxicity resulting in a loss of cell viability. Apremilast had no significant effect on UVB-induced cytotoxicity, but 10 µM apremilast significantly reduced the apoptotic effects of UVB radiation by ≈ 18% in HEKn cells, and TNF-α release. Apremilast significantly inhibited MEK cytotoxicity induced by UVB radiation by 20% and 23% at 0.1 and 10 µM, respectively.
T and B Cell Adaptive Transfer Model					
MDCG5	14 days	T/B cell	5 mg/kg	IgHb Mice	Apremilast did not have any significant effects upon the T cell activation markers CD69 and CD25, or alter CD86, CD40, or MHC II cells. Apremilast prevented the down regulation of CD62L on activated T cells amd CD80 expression on B cells. No effects on T cell proliferation or OVA-specific immunoglobulin (Ig) G1, IgG2a or IgMa production.

CIA = collagen-induced arthritis; ED50 = median effective dose; IP = intraperitoneal; LPS = lipopolysaccharide; mAb = monoclonal antibody; PO = oral; QD =daily; TNF-α = tumor necrosis factor-alpha.

Secondary pharmacodynamic studies

Apremilast (10 µM) was profiled for binding to 68 cell surface receptors and for inhibition of 17 enzymes (Report 8611). The results demonstrated that apremilast had no significant activity against any of the receptors or enzymes, except for 95% inhibition of PDE4, and 52% enhanced agonist binding of the L-type (verapamil) calcium channel receptor. However, results from a subsequent study (Report CC-10004-ET-151) confirmed that the 52% inhibition of the L-type (verapamil) calcium channel observed at 10 µM apremilast was a false positive hit. Kinase inhibition profiling of apremilast (10 µM) using Invitrogen's SelectScreen® Profiling Service demonstrated that the compound did not significantly inhibit any of the 255 kinases tested (Report SSBK8217-23649).

Assessment of Apremilast Binding to Human Cereblon

Human cereblon binding was investigated due to structural similarities between apremilast and thalidomide, namely the phthalimide moiety. The aminoglutarimide moiety which is responsible for thalidomide binding to cereblon is substituted for a di-alkoxyphenyl in apremilast. As cereblon binding is considered responsible for teratogenic effects associated with thalidomide, the comparative binding of apremilast to cereblon was investigated in competition studies of CRBN binding to thalidomide-analog affinity beads. Endogenous CRBN in human U266 MM cell extracts was incubated with varying concentrations of either apremilast, CC-5013 (lenalidomide, a thalidomide analog with an aminoglutarimide moiety) as a positive control for CRBN binding to the aminoglutarimide moiety, or dimethyl sulfoxide (1%) as the control vehicle. Apremilast at concentrations up to 100 µM did not compete for CRBN binding. In contrast, the positive control agent lenalidomide, successfully competed for CRBN binding with an IC50 value of approximately 3 µM.

Pharmacokinetics and Pharmacodynamics in the Rat and Ferret

Han Wistar rats were administered a single oral or intravenous dose of apremilast (1 mg/kg) and seven oral doses (10 mg/kg). The apremilast brain/plasma concentration ratio was ≤0.1, likely the result of apremilast being a P-glycoprotein substrate. Fasted ferrets received a single oral dose of apremilast (0.1 - 30 mg/kg). Ferrets were exposed to apremilast, with a plasma half-life of 3.8 hours. Apremilast concentrations (1-hour) were highest in ferret lung, followed by plasma, and finally brain, with brain/plasma ratios ranging from 0.11 to 0.15, similar to those of rats, and lung/plasma ratios from 1.4 to 3.5. A known pharmacological effect of PDE4 inhibitors is emesis (Robichaud, 1999). However, no emetic episodes were noted in ferrets dosed up to 3 mg/kg, and retching but no emesis in the 10-mg/kg dose group. The lack of emetic effects on ferrets is likely due to the poor penetration of apremilast across the blood/brain barrier. Additionally, apremilast inhibited pulmonary inflammation in the ferret as a result of higher apremilast concentrations in lung tissue.

Effect of Apremilast on Non-Hodgkin's Lymphoma B Cell Line

When non-Hodgkin's Lymphoma (Farage) cells were incubated with apremilast (0-100 µM) for 1 hour prior to the 6 hour ^{3}H-thymidine assay, weak antiproliferative activity was observed (approximately 20% inhibition of proliferation at 100 µM).

In vivo Animal Models and Supporting Studies

Table 3: In vivo animal models and supporting studies

Report Number	Treatment	Stimulus	Dose/ Route of	Study Type	Major Findings

	Duration		Administration	Species/ Sex	
Effects in Colitis Model					
Epistem 06-218c/ 07-163	4 days	TNBS	0.25 – 2.5 mg/kg BID PO	BDF1 mice Male	Weight loss was reduced in a dose-dep manner, diarrhea was reduced, mucosal damage reduced at 2.5 mg/kg. Apremilast had a positive trophic effect on crypt size. 0.25 mg/kg reduced myeloperoxidase activity. No effect on transcript levels of the TNF-α gene. Further gene expr analysis found no relationship between IFN-γ,Cxcl-9 Cxcl-10 and disease severity.
Effects in Lung Models of Inflammation and Asthma					
AP576, AP600, AP1025	4 hours post-LPS injection	LPS (100 µg/ mL)	0.1,0.3, 1, 3 mg/kg, PO, 1 hour before LPS	Rat/CD Females	Apremilast inhibited lung neutrophilia after LPS stimulation with an ED50 of approximately 0.25 mg/kg.
			0.003-0.1 mg/kg, IT, 30 mins before LPS		Apremilast administered intratracheally inhibited lung neutrophilia with an ED50 close to 0.003 mg/kg, which was ~100-fold more potent than oral administration.
121401	6 hours post-LPS exposure	LPS (100 µg/mL)	0.1. 30 mg/kg, PO, 0.5 hours before LPS exposure	Ferret Males	The apremilast threshold emetic dose was found to be 10 mg/kg, with an average of 0.5 emetic events (retches only) per ferret. The apremilast lung neutrophilia ED50 was . 0.8 mg/kg, thus yielding a therapeutic index of 12.
AP998R, AP1036R	5 days	OVA	1-25 mg/kg, PO, 1 hour prior to LPS on Day 17	Mice/BALB/c Males	Apremilast inhibited AHR by 59% at 1 mg/kg and by 91% at 25 mg/kg.
	9 days		10 mg/kg, PO, 1 hour prior to LPS on Day 17		Apremilast inhibited AHR by more than 96% at 24 and 48 hours, and by 83% at 72 hours post-OVA (Day 22) challenge. In addition, apremilast reduced lung levels of macrophages, neutrophils, lymphocytes, eosinophils, IL-4, RANTES, and eotaxin, and reduced plasma IgE levels.
DLXJ1000	4 days	OVA	3 and 30 mg/kg, PO, QD	Duncan-Hartley guinea pigs Males	Apremilast (3 mg/kg) pretreatment nonsignificantly reduced OVA-induced bronchospasms and 30 mg/kg had no effect.
1016668	< 1 hr	-	0.0001 – 1 µM (incubation)	Ex vivo, tissue bath of guinea pig, trachea	Apremilast produced a significant relaxation of guinea pig trachea under spontaneous tone contraction, with an EC50 = 310 nM
Effects in Gout-like Inflammation and Peritonitis					
MD-2-2-05-1168/ 9	8 hours	MSU crystals	2.5-12.5 mg/kg PO	BALB/c mice	No anti-inflammatory effects No reduction in gout-like peritonitis Trend towards TNF-α and MIP-1α reduction

Effect of Apremilast in Cellular Models of Cutaneous Lupus					
3252-910	18 hours	TLR9 agonist CpG-A	0.5-5 µM	In vitro HPBMCs	Significant inhibition of CXCL9, CXCL10, and CXCL11 gene expression
				pDC/HEKa coculture s	Inhibition of IFN-α and TNF-α protein production, HEKa intracellular MxA protein expression
Effect of Apremilast in Amyloid Lateral Sclerosis Model					
DRXL-001-CC-10004	~130 days	-	4-8 mg/kg/day	B6S JL-TgN(SOD1-G93A)dl 1 Gur mice	High dose delayed onset of ALS clinical symptoms, non-sig increased survival. Plasma concentrations of apremilast in fed mice were higher in females than in males. There was a small correlation between survival and plasma apremilast concentration
Effect of Apremilast in Bennett Model of Neuropathic Pain					
Report S07059	Post-surgery d12-15	CCI ligation	3 mg/kg, PO	DR rats	Pain was not reduced on Day 12 or Day 15

Safety pharmacology programme

The core battery of safety pharmacology studies were performed in line with ICH 7A, with an integrated cardiovascular and respiratory safety study in dogs. A gastrointestinal motility study was also performed in mice. The studies performed are outline in table 4 below.

Table 4: Summary of safety pharmacology studies

Organ Systems Evaluated	Species/Strain	Method of Admin.	Dose Duration	GLP	Study/Report Number
Central Nervous System	Mouse/CD-1	Oral gavage	0, 500, 1000, or 2000 mg/kg, single dose	Yes	1398/443
Cardiovascular and Respiratory	Dog/Beagle (anesthetized)	Intravenous	0, 0.5, 1, or 5 mg/kg, three ascending doses at least 30 minutes	Yes	1398/264-D6146
Cardiovascular hERG	Human embryonic kidney cells (HEK-293)	In vitro	0, 16.8, 49.7, 87.5, or 249.7 uM, ≈3 minutes	Yes	031206.DFN
Gastrointestinal tract	Mouse/CD-1	Oral gavage	0, 10, 100, or 1000 mg/kg, 30 minutes	Yes	CC-10004-TOX-1171

Mouse Central Nervous System and Behavioral Studies Using the Irwin Screen

A GLP-compliant Irwin study was performed in Crl:CD-1(ICR)BR mice to assess apremilast CNS safety following oral gavage administration of 500, 1000, and 2000 mg/kg (Report 1398/443). Observations were performed up to 300 minutes post dose and general observations continued up to 7 days. At 1000 mg/kg, apremilast produced signs of lacrimation and ptosis, which were slight in severity and of short duration, generally appearing 60 minutes post-dose and were gone by the 300 minutes timepoint. At 2000 mg/kg clinical signs included apathy, lacrimation, and ptosis, occurring within the same time-frame as those effects seen at 1000 mg/kg, but persisting in one animal at 300 minutes post-dose. One animal in the 2000 mg/kg group died on day 2. Piloerection was seen in one animal at day 2. Toxicokinetic

parameters were not measured but are extrapolated from a previous study in Crl:CD-1(ICR)BR mice. At 500, 1000 and 2000 mg/kg, Cmax values of 8650; 9184; and 11,940 ng/mL, respectively. The corresponding area under the plasma concentration-time curve (AUC) values were 112,640; 117,290; and 158,315 ng·h/mL. The NOEL level of 500 mg/kg provides 12.9 and 15.4 fold safety margin based on C_{max} and AUC respectively, from the 30 mg BID clinical apremilast dose.

Cardiovascular and Respiratory Effects in Anesthetized Dogs

Cardiovascular and respiratory safety was determined in a GLP study in anesthetized dogs following intravenous administration of apremilast in ascending doses from 0.5 – 5 mg/kg (Report 1398/264-D6146). 0.5 mg/kg elicited a small (9%) increase in left ventricular maximum rate of change (dP/dtmax) 2 min after dosing. This increase was sustained until administration of the next dose, and was significantly different from the vehicle treated group. This effect was not considered adverse. No other effects in cardiovascular parameters were apparent at this dose. At 1.0 mg/kg heart rate was significantly increased by 28% from 2 min after dosing and returned to baseline at 30 mins, and was reflected in decreased RR and QT intervals. Corrected QTc was not affected. dP/dtmax was also significantly increased by 29%, which also returned to baseline before subsequent doses. 5 mg/kg elicited further increases in heart rate of 82% from baseline and dP/dtmax to 74% from baseline 45 min post-dose. The tachycardia also resulted in corresponding decreases in the RR and QT intervals. QTc was not noticeably affected. These effects were statistically significant, and returned to baseline within 45 minutes. There was a small transient increase in mean arterial blood pressure that was not significant.

There were no noticeable differences in the rate and depth (tidal volume) of respiration between the vehicle and test article treated groups at any dose level. However, apremilast elicited an apparent dose related increase in Peak Inspiratory Flow (from a baseline of 248 mL/s to 429 mL/s 90 min post-dose 3) and Peak Expiratory Flow (from a baseline of 330 mL/s to 461 mL/s 120 min postdose 3) throughout the duration of the study. Statistical analyses suggest that the increase in peak inspiratory flow was significantly different (10 and 60 min post-dose 3) from the vehicle treated group.

Mean Cmax values (male and female combined) at 2 minutes after the end of infusions were 662, 1277, and 5074 ng/mL at dosages of 0.5, 1, and 5 mg/kg, respectively. The no-observed-adverse-effect-level (NOAEL) was 0.5 mg/kg (mean Cmax value is 1-fold clinical Cmax of 670 ng/mL). There was no treatment-related effect on QTc interval up to and including the highest dose of 5 mg/kg, which provides a 7.6-fold safety margin from the clinical Cmax.

Measurement of Ionic Currents in Cloned hERG Genes Expressed in Mammalian Cells

Potential for effects on QTc parameters was investigated in a GLP *in vitro* hERG assay in voltage-clamped human embryonic kidney (HEK-293) cells (Report 031206.DFN). Apremilast inhibited hERG current by (mean ± SEM) 6.3 ± 0.9% (n = 4) at 16.8 µM, 19.3 ± 1.4% (n = 3) at 49.7 µM, 28.5 ± 0.6% (n = 3) at 87.5 µM, and 59.0 ± 1.7% (n = 4) at 249.7 µM; vehicle control reduced hERG current by 1.6 ± 0.3% (n = 3). The IC50 for the inhibitory effect of apremilast on hERG current was estimated to be 184.2 µM (84.8 µg/mL); (Hill coefficient = 1.1); this represents a margin of 127-fold over the Cmax in psoriasis patients at the maximum recommended therapeutic dose of 30 mg BID.

Effects on Gastrointestinal Motility in Mice

A GLP-compliant study in mice was performed to determine the effects of oral apremilast on gastrointestinal motility in male CD-1 mice (Report CC-10004-TOX-1171). Animals were given 10, 100, and 1000 mg/kg. Approximately 30 minutes after vehicle or dose administration, all animals were given a charcoal suspension. Animals were euthanized by decapitation 30 minutes (± 3 minutes) following charcoal administration and the intestinal tract was quickly excised. The distance traveled by the charcoal

suspension was measured along with the total length of the small intestine to determine the effects of CC-10004 on gastrointestinal motility. A single oral (gavage) administration of CC-10004 to male Crl:CD-1 mice did not affect the percent distance traveled of the charcoal suspension or normalized percent inhibition of travel at 10, 100, or 1000 mg/kg. Based upon the lack of effect on gastrointestinal motility in this study, the No-Observed-Effect Level (NOEL) was 1000 mg/kg, the highest dose administered. Toxicokinetic parameters were not measured.

Pharmacodynamic drug interactions

Prostaglandin E2 binds to prostanoid receptors on monocytes, T cells and other leukocytes, elevating intracellular cAMP levels resulting in inhibition of cellular responses. The combination of PGE2 and apremilast dose-dependently and synergistically elevated cAMP levels in HPBMCs and neutrophils demonstrating enhanced PGE2-mediated elevation of cAMP in both HPBMCs and neutrophils. Apremilast was also found to inhibit GM-CSF production by normal human lung fibroblasts in a screen of 23 PDE4 inhibitors. Apremilast in combination with forskolin inhibited TNF-α mediated GM-CSF production with an IC_{50} of 0.12 µM.

A study examining the effects of apremilast alone and in combination with PGE2 on TNF-α-induced E-selectin and other adhesion molecules expressed in HUVECs demonstrated that the apremilast/PGE2 combination significantly inhibited TNF-α induced E-selectin and vascular cell adhesion molecule 1 (VCAM-1). However even under TNF-α stimulated condition which serves to boost marker expression, the overall change in adhesion marker cell surface expression remains modest, and was generally similar to PGE2 alone. However, in the presence of PGE2, E-selectin, and VCAM-1 inhibition may be a potential apremilast mechanism of action as an antiangiogenic and anti-inflammatory agent.

In a study of apremilast in combination with indomethacin or methotrexate, apremilast was evaluated in the collagen-induced arthritis DBA/1 mouse model. Overall in this study, apremilast did not cause any antiarthritic effect when administered alone, despite the fact that some reductions in paw scores and measurements were noted. In a further mechanistic study, apremilast did not increase the percentage of IL-17 producing cells present in inguinal lymph nodes, but did increase IFNγ and IL-6 levels.

The effects of combining apremilast with cyclosporine A (CsA), etanercept (ETC) or methotrexate (MTX) for the inhibition of cytokines associated with rheumatoid arthritis (RA) and psoriasis (Pso) was assessed in human anti-CD3 monoclonal antibody (mAb)-stimulated T cells and staphylococcal enterotoxin B (SEB)-treated PBMCs. In the stimulated T cells derived from a donor with high cytokine levels, the combination effect of apremilast with CsA synergistically inhibited IFN-γ, IL-10, IL-13, IP-10, MIP-1α, MIP-1β, and TNF-α production at a minimum of one of the tested concentrations. IL-4 was increased with the apremilast /CsA combination, whereas Il-2 production was decreased. The apremilast/ETC combination synergistically inhibited IFN-γ, IL-13, IP-10, MIP-1α, MIP-1β, and TNF-α production at a minimum of one of the tested concentrations and non-additively inhibited IL-2 and IL-4 production.

In the human NK cell-driven model of psoriasis utilizing human skin xenotransplanted onto immunodeficient mice, the combination of 1 mg/kg MTX with apremilast (5 mg/kg; PO divided into two daily doses of 2.5 mg/kg) exhibited a modest therapeutic effect in 2 of 5 mice. Recovery was improved in animals receiving 2 or 3 mg/kg MTX alone, however adverse effects were seen at the highest dose leading to death, whereas this was not seen in combination. Immunohistochemical staining for TNF-α also showed less TNF-α expression in combination treated tissue than control, and a similar level to tissue from mid/high dose MTX.

2.3.3. Pharmacokinetics

The absorption, distribution, metabolism, and excretion characteristics of apremilast (S enantiomer) have been investigated in vitro and in vivo in the animal models used for toxicity testing. In vitro studies have been performed to assess the potential for drug-drug interactions. No evidence of interconversion between apremilast and its R-enantiomer was observed in vivo. Appropriate achiral and chiral analytical methods were developed and suitably validated to quantify apremilast (S enantiomer), its R enantiomer (CC-10007), and its metabolites in plasma of animal models used in pre-clinical pharmacokinetic and toxicity studies.

Absorption

Pharmacokinetics, absorption and oral bioavailability of apremilast or [14C]-apremilast-derived radioactivity was evaluated in mice, rats, rabbits and monkeys.

Mouse

Following IV dosing plasma concentrations of apremilast declined steadily, falling below the limit of quantification by 12 h and 24 h in males and females respectively. AUC and $T_{1/2}$ values indicate total radioactivity persisted, indicating persistent metabolism. Radioactivity was cleared more slowly in females. Following oral dosing at 500 mg/kg, apremilast was still quantifiable at 48 h with a longer $t_{1/2}$ compared to iv doses. Concentrations of radioactivity were significantly higher than those of apremilast at each time point, consistent with the presence of metabolites. No significant sex-related differences were observed. Oral bioavailability ranged from approximately 20% to 33% for apremilast and for radioactivity. For both dose routes, concentrations of radioactivity in blood were consistently lower than those in plasma at the same time point, indicating that there was no specific association of apremilast or its metabolites with blood cells.

In a bile-duct cannulated male mouse study following a single 10 mg/kg oral dose of [14C]-apremilast, 54% and 16% of the radioactive dose was excreted via the biliary and urinary routes, suggesting that at least 70% of the radioactive dose was absorbed in mice, indicating apremilast is subject to moderate first pass metabolism. Toxicokinetic evaluation in mice suggests exposure increases dose-proportionally and less than dose-proportionally at doses over 100 mg/kg/day. The studies do not indicate sex-related differences or inversion of apremilast to its R enantiomer in mice.

Rat

Following IV dosing, plasma concentrations declined steadily in both males and females, but concentrations were below the limit of quantification by 8 h after dosing in males animals but still detected at 24 h in females. Sex differences in exposure were also reflected in the lower AUC and shorter $t_{1/2}$ values in males compared with females, and systemic clearance was high in males and low in females. Following oral dosing at 50 mg/kg in males and 10 mg/kg in females, exposure was 6-fold greater in females. AUC values indicated oral bioavailability of 11.5% and 64.8% in males and females respectively. Similar sex differences in exposure were observed following IV or oral administration of CC-7085 (racemate) or CC-10007 (R enantiomer) as compared to following administration of apremilast.

In a second oral study, concentrations of both total radioactivity (e.g., parent compound plus any metabolites) and of parent compound in plasma were greater in females than in males. In males, the total radioactivity AUC values were 25 to 96 times greater than those for parent compound, whereas in females the difference was only 2- to 3-fold, suggesting that metabolism was more extensive in male than in female rats. In the same study following six daily doses, accumulation was indicated by C_{max} and AUC values in females, but not in males.

In a study of the effect particle size in fasted, apremilast AUC and C_{max}, as well as other pharmacokinetic parameters, were similar in rats dosed with micronized and milled drug substance indicating particle size does not affect the pharmacokinetics of apremilast in male rats. Measurement of apremilast's R enantiomer indicated no chiral inversion occurs in rats.

Rabbit

In female New Zealand White rabbits following a single 1000 mg/kg oral dose, apremilast was rapidly absorbed. In pregnant female New Zealand White rabbits infused 10 mg/kg apremilast, following termination of infusion apremilast concentrations declined rapidly with a mean half-life of 1.2 h. The mean plasma clearance was high (2039 mL/h/kg), which is greater than 50% of the hepatic blood flow in rabbits. The volume of distribution was moderate (1843 mL/kg) and was approximately 2.5 times the total body water volume. Following a 250 mg/kg oral dose exposure was negligible, with a mean Cmax of 2.62 ng/m and an absolute oral bioavailability of less than 0.02%. The AUC ratio of CC-10007 to apremilast was approximately 0.02, which is similar to the level in the administered dose.

In a third study, 12 non-mated female New Zealand White rabbits were administered either 250 mg/kg/day apremilast via stomach tube, 25 mg/kg/day apremilast via a 2-h IV infusion, 25 mg/kg/day apremilast via subcutaneous injection, or vehicle via a 2-h intravenous infusion for three days. Following IV administration to apremilast had a high clearance (> 3000 mL/h/kg) and large volume of distribution (> 3 L/kg). Exposure was minimal following oral dosing, with bioavailability less than 0.1%, compared to over 95% with subcutaneous dosing. The low exposure following oral dosing is consistent with in rabbit studies.

Monkey

Cynomolgus monkeys were administered a single IV dose of 1 mg/kg, followed by a washout and further oral dose of 10 mg/kg. Following IV dosing, concentrations of apremilast in plasma were significantly lower than those of total radioactivity at 5 and 10 min after dosing and had fallen below the lower limit of quantification (i.e., 75.0 ng/mL) within 30 min of dosing. Apremilast concentration data were insufficient to carry out pharmacokinetic analysis. The higher concentration of total radioactivity compared to apremilast and the much shorter half life of unchanged drug are consistent with extensive metabolism. Blood plasma concentration ratios for total radioactivity were generally in the region of 0.6:1 and did not change with time. This indicates that drug-related material moderately penetrated the blood cells.

Following oral administration, bioavailability was estimated at 80% based on radioactivity, as IV apremilast exposure could not be quantified. Absorption appeared to be rapid, with T_{max} reached within 1 hour. There were no notable sex-related differences in the pharmacokinetics of apremilast in monkeys.

Distribution

Tissue distribution in mice following oral and IV administration of [14C]-apremilast and plasma protein binding of apremilast were evaluated. Placental transfer of apremilast was evaluated in mice and the lacteal excretion in mice and monkeys.

Tissue Distribution

The tissue distribution of [14C]-apremilast-derived radioactivity in the male and female albino mice (CD-1 strain) and the male pigmented mouse (B6C3F1 strain) has been investigated. For tissue distribution, each animal received a single oral (gavage) dose, at nominal dose level of 500 mg/kg. The tissue distribution of the parent-derived radioactivity was evaluated by quantitative whole-body autoradiography at up to 168 hours post-dose.

Initial distribution was highest in the gastrointestinal mucosa, liver, kidney, and pancreas, with lower levels in the secretory glands and reproductive tissue in both males and females. Radioactivity was detected in the CNS in both males and females for up to 24 hours. In albino mice, by 72 h after dosing, levels had fallen below the lower limit of quantification (0.71 µg eq/g) except for the liver and, in males only, the kidney (cortex and medulla), skin, uveal tract, nasal mucosa, and gastrointestinal mucosa. Subjective assessment of the levels of radioactivity was made for those tissues where full quantification was not possible. Radioactivity was detected in the kidney pyramid up to 24 h after dosing and in the urinary bladder contents, gall bladder, esophagus, and gastrointestinal tract contents up to 72 h. Radioactivity was not detected in any tissues at 168 h after dosing or later. In pigmented mice, levels of radioactivity were elevated in the uveal tracts of the eyes compared to albino mice at 1 and 3 days post-dose. Low levels of radioactivity were observed in most tissues 3 days after dosing but levels were below the lower limit of quantification by 7 days post dose.

Quantitative whole-body autoradiography demonstrated that the absorbed radioactivity was rapidly distributed into the tissues, although the concentrations measured were generally low. The highest levels of radioactivity were generally associated with the principal organs of biotransformation and excretion (e.g., the liver and kidney) and the pancreas. Significant levels of radioactivity were also present in the gall bladder up to 72 h after dosing, providing further evidence of biliary elimination. The concentrations measured in the central nervous system were consistently low, indicating that penetration of the blood/brain barrier was poor. The pattern of tissue distribution observed in male and female albino mice was generally similar at comparable sampling times. There was no significant association of radioactivity with melanin-containing tissues (e.g., uveal tract and pigmented skin) in pigmented male animals.

In vitro Plasma Protein Binding

Protein binding of apremilast was determined in vitro in plasma of mouse, rat, rabbit and monkey, human healthy volunteers and human plasma ultrafiltration. Protein binding of apremilast was conducted in triplicate at concentrations of 0.25, 0.75, and 2.5 µg/mL at room temperature, and analyzed using LC-MS/MS assay. The overall mean apremilast percent bound was 88.6 ± 2.3% in mouse plasma, 90.6 ± 0.9% in rat plasma, 80.9 ± 1.2% in rabbit plasma, 84.3 ± 1.5% in monkey plasma, and 68.3 ± 0.9% in human plasma in the tested concentration range of 0.25 to 2.5 µg/mL. Overall, apremilast was moderately protein-bound in plasma of animals and human, and the binding was concentration-independent in the tested concentration range of 0.25 to 2.5 µg/mL. Plasma protein binding was lower in humans compared to animals.

Placental Transfer

As part of fertility and developmental toxicity study in female CD-1 mice and an embryo-fetal development study in cynomolgus monkeys, the transport of apremilast across the placenta was assessed. In mice, following daily oral administration of apremilast beginning 15 days prior to cohabitation and continuing through Day 15 of presumed gestation at doses of 10, 20, 40, and 80 mg/kg/day, blood was collected from pregnant mice (n = 3/time point) at 0.5, 2, 4, 8, and 24 h postdose on gestation Day 15. Blood was collected from fetuses) at the time of sacrifice in the 24 h postdose mice. Maternal plasma apremilast concentrations increased in a less than dose proportional manner. The fetal plasma concentrations at 24 h were highly variable, with six of the ten litters evaluated being below the limit of quantification (1 ng/mL). In fetal plasma from four of the ten litters evaluated, apremilast was quantified, with concentrations ranging from 14.5 to 2813 ng/mL. The mean fetal-to-maternal plasma concentration ratios ranged from 0.3 to 1.07, indicating apremilast crossed the placenta in mice.

In monkeys, pregnant animals were administered daily oral doses of apremilast beginning on gestation day 20 through gestation day 50, and a single oral dose on gestation day 100 at dosages of 20, 50, 200,

and 1000 mg/kg/day (n = 16/group at the beginning of the study). Maternal and fetal blood was collected at 5 h postdose on gestation Day 100. In all dosage groups, the fetal-to-maternal plasma concentration ratios were between 0.3 and 0.4, indicating apremilast crossed the placenta in monkeys.

Lacteal Excretion

The lacteal excretion of apremilast was evaluated following oral administration of apremilast to lactating CD-1 mice. In this study, female mice approximately 13 days postpartum received a single oral dose of apremilast at 10 mg/kg, administered by oral gavage in a volume of 10 mL/kg. Milk and blood samples from 5 animals per time point were obtained at 1, 6, and 24 h postdose and apremilast concentrations determined in plasma and milk using LC-MS/MS analysis. The mean apremilast plasma concentrations at 1 and 6 h postdose were 984 and 138 ng/mL, while concentrations in milk were 1441 and 186 ng/mL, respectively. The resulting mean milk-to-plasma ratios ranged from 1.46 to 1.62, indicating transfer of apremilast into milk in mice. Plasma and milk concentrations were below the detection limit of 3 ng/mL in the 24-h samples.

Metabolism

In vitro and in vivo metabolism of apremilast was investigated in mice, rats, female rabbits, monkeys and humans.

Metabolism by Liver Microsomes

This study was conducted to identify the in vitro metabolic pathways of [^{14}C]-apremilast in male and female mouse, rat, rabbit, dog, monkey and human liver microsomes.

At 10 µM [^{14}C]-apremilast the apparent rank order of extent of apremilast metabolism was rabbit >> monkey > mouse = male rat > human > dog > female rat. No sex differences were observed in any species except rat. The major metabolite of both apremilast and CC-10007 in human liver microsomes was M3 (10% of radioactivity). M7 (1.8%) was identified in the absence of β-NADPH suggesting no CYP450 involvement.

The major metabolite, M3, observed in all test incubations, with the notable exception of female rat, was identified as the *O*-desmethyl metabolite. A sex difference in metabolism was therefore apparent in rat. M3 was the only CYP-dependent metabolite observed in dog, human, and male rat. An additional metabolite, M5, was observed in mouse and monkey, which co-chromatographed with the *O*-desethyl metabolite reference standard CC-10047. A number of other minor metabolites, M4, M8, M9, and M10, were observed in rabbit, in addition to M7.

The *N*-deacetylated product (M7) was formed to a minor extent in the absence of NADPH in mouse, dog and human liver microsomal incubations, and to a greater extent in the presence of rabbit liver microsomes. It appears that this non-CYP mediated hydrolysis of the amide bond is favourably catalyzed by rabbit liver microsomes compared to other species.

Metabolism by Hepatocytes

In vitro metabolism of [^{14}C]-apremilast was investigated in mouse, rat, rabbit, dog, monkey and human hepatocytes.

[^{14}C]-apremilast was not stable in the incubation media. After 4-hr incubation without hepatocytes, only 69.0-73.2% of [14C]-CC-10004 remained unchanged. Significant hydrolysis products M1/M2 and M18 were observed, accounting for 13.3-13.9% and 11.6-13.0%, respectively. In addition, multiple minor radioactivity peaks were also present in the negative control samples, accounting for 1.9-4.1%.

[^{14}C]-apremilast was metabolized extensively by rabbit hepatocytes, moderately by rat hepatocytes, and to a limited extent by hepatocytes from the mouse, dog, monkey, and human. Unchanged [^{14}C]-apremilast and 12 metabolite peaks (M1/M2, M3, M4, M7, M11, M12, M14, M15, M16, M17, M18, and M23) were characterized and/or identified by LC-MS/MS, production scan, and/or MS/MS in the MRM mode. M1/M2 and M18 showed a similar or lower percent of the total radioactivity in all hepatocyte incubations compared to the negative control sample. A high concentration of M14 was observed in rabbit hepatocyte incubations, accounting for 25.4% to 29.7% of the total radioactivity. A much lower amount of M14 was observed, ranging from 0.8% to 2.6% of the total radioactivity in the hepatocyte incubations of the other five species. M3, M7, and M12 were observed in the hepatocyte incubations of all species. The other minor metabolites showing detectable radioactivity were M4 (in mouse, rat, and rabbit hepatocyte incubations), M15 (in rat, rabbit and monkey hepatocyte incubations), M16 (in mouse, rat, and human hepatocyte incubations), and M17 (in mouse, rat, and human hepatocyte incubations). Some metabolites were present at very low levels and were detectable by only LC/MS. Overall, all the metabolites formed in vitro by human hepatocytes were formed by hepatocytes from one or more animal species.

In Vitro Juvenile Metabolism in Mice and Humans

[14C]-Apremilast was hydrolyzed in control incubations without microsomes or hepatocytes to produce M1 and M2 (hydrolysis products), as well as M18 (3-acetamide-phthalic acid). Metabolites identified in human microsomes and hepatocytes included M3, M7, M11, M12, M13, M14, M15 and M17. There were no notable qualitative differences between the metabolite profiles in the adult human liver microsomes (pooled mixed gender) versus the juvenile male and juvenile female liver microsomes. Similarly, for human cryopreserved hepatocytes, there were no notable differences observed between the adult (pooled mixed gender) versus juvenile male and female hepatocytes. In adult and juvenile mouse liver microsomes there were no notable differences between the profiles generated, except for M7, which was formed by adult to a very minor extent.

In Vivo Metabolism

In vivo metabolism was evaluated in mice, rats and monkeys and to a limited extent in female rabbits.

Mouse

In mice following oral dosing, metabolite profiles were qualitatively similar in plasma, urine and faeces. In plasma at the early time points, apremilast was the largest peak (except in females after oral dosing). At the later time points, the proportion of radioactivity associated with parent compound decreased, with a corresponding increase in that associated with metabolites. Hydrolysis products M1 and M2 were the major components of plasma radioactivity. Metabolite M15 metabolite was also present at significant amounts. Parent drug was higher in faeces following oral doses than IV doses. In orally dosed males/females excreted dose was accounted for by 5.6%/7.2% of M1/M2, 8.4%/6.2% of M3, 14.4%/12.6% of M9, 0.9%/0.5% of M12, 5.3%/5.2% of M19 and 2.2%/7.0% of M22.

In bile duct cannulated mice following 10 mg/kg oral or 5/10 mg/kg IV doses unchanged apremilast and M12 were the major plasma components as well as M13, M14 and trace metabolites. Bile was the major excretion route with 53.9% and 59.1% of dose recovered from oral and IV groups at 48 h. The major biliary metabolites were M12 and M13, accounting for approximately 30% and 10% of the dose, respectively. An average of 15.1% and 17.8% of dose was recovered in urine with M12 and M13 the most abundant. An average of 15.6% and 10.5% of the dose was recovered in faecal samples at 48 h with parent drug and M3 present at the highest levels. The study indicates apremilast absorbed following an oral dose is extensively metabolized prior to elimination and primarily excreted via the biliary route.

Rat

Following oral administration of 10 mg/kg [^{14}C]-apremilast, little or no apremilast was observed in male rats. The principle metabolite in male rats was not identified, and M12 was a major plasma component, which were both also present in females as well as M1/M2 which was predominant. In urine the profiles were similar in both sexes. The principle metabolite was M12. The principle metabolite in faeces was M3 in both sexes, although present at higher levels in males. Other notable metabolites in rat excreta include M5, M7, M8, and M9, representing 0.36% to 8.59% of the radioactive dose.

Rabbit

Following oral doses of 1000 mg/kg, the plasma levels of apremilast was below the limit of detection. No metabolites were detected. One animal's plasma gave mass spectra consistent with a glucuronic acid conjugate of *O*-desmethyl-apremilast.

Monkey

Apremilast was the predominant component of the circulating radioactivity at the early time point but decreased with time, while metabolites were the major components at 24 h postdose. The metabolites observed in plasma include M1, M2, and M12, in addition to two polar metabolites (MkP2 and MkP3), which could not be identified due to interference from high levels of endogenous material. Two other minor metabolites were identified as the two isomers of M15 (*O*-desmethyl hydrolyzed apremilast glucuronide). Little or no apremilast was excreted in urine. The major urinary metabolite was M12. Only low levels of unchanged apremilast were present in faeces, even after oral dosing. The principle metabolites in faeces were M3 and two isomers of M9. Minor metabolites were identified as M19 and M10.

Excretion

The rates and routes of excretion of radioactivity after IV and/or oral administration of [14C]-apremilast was evaluated in mouse with and without bile duct cannulation, rats and monkeys. The recovery data are summarised in table 5 below.

Table 5: Excretion of radioactivity following a single dose of [^{14}C]-Apremilast

Species	N	Dose (mg/kg)	Route	Sex	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Recovery (% dose)	Time (h)
Mouse		10	IV	M	7.8	66.2	NC	90.6	48
		10	IV	F	8.7	71.3		91.1	
		500	PO	M	4.1	71.5		97.7	
		500	PO	F	3.0	73.1		92.8	
Mouse (BDC)		5	IV	M	17.8	10.5	59.1	90.2	48
		10	PO	M	15.1	15.6	53.9	91.0	
Rat		10	PO	M	8.5	33.4	NC	45.4	24
		10	PO	F	12.1	44.5		60.8	
		10	PO	M	15.7	57.9		74.5	
		10	PO	F	29.6	28.2		52.6	

Monkey	1	IV	M	15.7	56.6	NC	79.6	168
	1	PO	F	16.2	56.0		81.1	
	10	IV	M	17.2	69.3		93.5	
	10	PO	F	20.3	68.2		95.8	
Human	20	PO	M	57.9	39.2	NC	97.1	

Pharmacokinetic drug interactions

In vitro studies have been conducted to examine the role of CYP isozymes in the oxidative metabolism of apremilast. The potential inhibitory and inductive effects of apremilast on CYP activities in vitro were also evaluated. Apremilast was also evaluated in vitro as a potential inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3. Additionally apremilast was evaluated as a potential inhibitor of MRP1, MRP2, MRP3, MRP4 and MRP8 in vitro.

Cytochrome P450 Reaction Phenotyping

In human liver microsomes, [^{14}C]-apremilast was metabolized to four products, designated as M1, M2, M3, and M5. Metabolites M3 and M5 were not produced to an appreciable extent in the absence of NADPH, indicative of the involvement of CYP enzymes. The apparent Km values for M3 and M5 were high (199 and 194 µM, respectively) suggesting that [^{14}C]-apremilast has a relatively low affinity for these isozyme.

Following incubations with cDNA expressed human P450 isoforms, CYP3A4 was found to be capable of efficiently metabolizing apremilast to M3, and CYP2C8 and CYP2D6 to a small extent. Apremilast was metabolised to M5 predominantly by CYP3A4 and CYP2A6 and to some extent by CYP1A2.

Marked inhibition of the formation of M3 and M5 was observed following incubation in the presence of the selective CYP3A4 inhibitor ketoconazole (59% for M3, 104% for M5). These data generally support the data generated with recombinant CYP3A4, confirming that apremilast metabolism was mediated via CYP3A4 to a major extent. Notable inhibition was also observed for M3 and M5 for furafylline (CYP1A2), M5 for 8-methoxypsoralen (CYP2A6), and to a lesser extent, monoclonal anti-CYP2E1, sulphaphenazole (CYP2C9), and tranylcypromine (CYP2C19).

In summary, the results of the present study indicate that the metabolism of [14C]-apremilast is mediated predominantly by CYP3A4, although other isozymes, such as CYP1A2 and CYP2A6, may contribute to a lesser extent to the metabolism.

Inhibition of Cytochrome P450

Studies were conducted to investigate the inhibitory and time-dependent effects of apremilast on selected P450 activities in human liver microsomes. Apremilast did not significantly inhibit marker enzyme activities for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at any concentration evaluated. Apremilast was a weak direct inhibitor of CYP2C8, estimated half-maximal inhibition (IC50) of 56.1 µM. Based on these in vitro results and the plasma concentrations of apremilast observed at clinically relevant doses, apremilast is unlikely to cause drug-drug interactions due to enzyme inhibition when coadministered with substrates of these CYP isoforms.

Induction of Cytochrome P450

The potential for apremilast to act as an inducer of CYP enzymes was evaluated in primary cultures of human hepatocytes with subsequent determinations of microsomal CYP activities. Under the conditions of

this study, treatment of cultured human hepatocytes with prototypical inducers caused the anticipated increases in CYP activity. Treatment of cultured human hepatocytes with apremilast at 10 and 100 µM caused a concentration-dependent decrease in microsomal 7-ethoxyresorufin O-dealkylase (CYP1A2) and diclofenac 4′-hydroxylase (CYP2C9) activity. The decrease in CYP1A2 and CYP2C9 activity was 35% at 10 µM apremilast, and 45% to 73% at 100 µM. In general, treatment of cultured human hepatocytes with apremilast had little or no effect on CYP2B6 or CYP2C19 activity. However, for CYP2B6, there was a trend toward an increase in activity, and in the case of CYP2C19, there was a concentration-dependent decrease in two cultures and a concentration-dependent increase in the third culture. Treatment of cultured human hepatocytes with apremilast caused an increase (3.7-fold) in testosterone 6β-hydroxylase (CYP3A4) activity, and the increase was statistically significant at the highest concentration (100 µM apremilast). At 100 µM, apremilast was about half as effective as rifampin at inducing CYP3A4 activity.

Apremilast had no effects on CYP1A2 and CYP2C9 at 1 µM; treatment at higher concentrations caused 35% (10 µM) and up to 70% (100 µM) decreases in CYP1A2 and CYP2C9 activities. There was no effect on CYP3A4 activities at 1 and 10 µM apremilast. A 3.7-fold induction of CYP3A4 (roughly half the extent induced by rifampin) was observed at 100 µM. However, this effect is unlikely to be clinically relevant because 100 µM is approximately 70-fold higher than observed Cmax of apremilast in psoriasis patients following 30 mg BID dosing (approximately 1.5 µM).

Interaction with P-glycoprotein

The intrinsic permeability of apremilast and its interaction with xenobiotic transporter P-gp as a substrate and as an inhibitor were assessed in control and human P-gp expressing LLC-PK1 cell lines. The determined intrinsic apparent permeability (Papp) value was 21 x 10^{-6} cm/sec across native LLC-PK1 monolayer following a 120-minute incubation, which is considered moderate. Bidirectional permeability determinations in control and P-gp-expressing cells demonstrated that apremilast was transported by P-gp, based on net efflux ratio of 27 (after 120-minute incubation). The transport activity of 10 µM apremilast was assessed in the absence and presence of ketoconazole, a known inhibitor of P-gp. Ketoconazole inhibited apremilast transport by 92%. These results further support the evidence that apremilast is actively transported by P-gp.

Apremilast was evaluated as an inhibitor of P-gp. The results demonstrated that apremilast has no significant inhibitory effect on the transport of P-gp substrate digoxin at apremilast concentrations ≤ 20 µM, and could potentially be a weak inhibitor at ≥ 50 µM (less than 50% inhibition at 50 µM). At the highest planned clinical dose of 30 mg, concentrations of apremilast could reach 260 µM (30 mg/250 mL) in the intestine. The resulting ratio of apremilast concentration (260 µM) to P-gp IC50 (> 50 µM) is <5, suggesting apremilast is unlikely to significantly inhibit P-gp in the gastrointestinal tract (Zhang, 2008).

Interaction with Other Drug Transporters

Apremilast had little or no inhibition of OAT1- or OAT3-mediated uptake at the 2 and 10 µM. At up to 20 µM, apremilast did not inhibit BCRP-, MRP1-, MRP2-, MRP4-, OCT2-, or OATP1B3-mediated transport. Weak inhibition (< 30%) of MRP3 (at 2 and 20 µM apremilast) and OATP1B1 (at 20 µM apremilast) was observed, but is unlikely to result in clinically relevant inhibition of these transporters. Apremilast did inhibit MRP8-mediated transport, with 42.7% and 59.8% inhibition, at 2 and 20 µM, respectively. The clinical relevance of this inhibition is unclear because the role of MRP8 in drug disposition is not clearly understood.

In studies to determine whether apremilast is a substrate for a range of transporters in relevant cell lines, bidirectional permeability and/or cleared volume data indicated apremilast is not a substrate for BCRP, OAT1, OAT3, OATP1B1, OATP1B3 or OCT2.

2.3.4. Toxicology

The nonclinical safety program of apremilast (CC-10004) consisted of single-dose toxicity studies in mice and rats (oral and intravenous), a series of repeat-dose toxicity studies for dosing durations up to 6 months in mice and 12 months in monkeys, genotoxicity core battery studies (in vitro Ames and chromosome aberration and in vivo micronucleus assays), carcinogenicity studies in mice and rats including 3-month maximum tolerated dose (MTD) studies to select the dosages for 2-year carcinogenicity studies, reproductive and developmental toxicity studies in mice and monkeys, and local tolerance studies. A study to compare the toxicity profiles of S enantiomer (apremilast) and R enantiomer (CC-10007) in rats was also conducted. In addition, a mechanistic study was conducted to investigate the time course for development and recovery of inflammatory lesions observed in multiple tissues of mice and to examine potential biomarkers for proinflammation response. The phototoxicity potential of apremilast was assessed in an in vitro assay in 3T3 fibroblast cells. A dosage-range-finding study and a pivotal 13-week toxicity study in juvenile mice were also conducted.

Single dose toxicity

The study design and major findings are summarised in table 6 below.

Table 6: Single dose toxicity studies

Study	Species/ Sex /Number/ Group	Dose/Route (mg/kg)	MLD/MNLD (mg/kg)	Major findings
1398/278	Mouse/Crl:CD-1 (ICR)BR 5/sex	2000 (preliminary and main) Oral	>2000	No body weight effects or gross macroscopic necropsy findings Isolated palpebral closure
1398/279	Mouse/Crl:CD-1 (ICR)BR 5/sex	Preliminary: 50, 75, 100, 150, or 200 Main: 120 IV	MLD: 120 Males >120 Females	Mortality at 150 and 200 mg/kg (prelim) Clinical signs ≥ 50 mg/kg tachypnoea, lethargy and palpebral closure Mortality in 1 M 120 mg/kg Tachypnoea, palpebral closure (males)
1398/276	Rat/Crl:WI(G1x/ BRL/Han)BR 5/sex	Preliminary: 200, 400, 700, 1000, 1500, or 2000 Main: 300 (F) or 2000 (M) Oral	MLD: 2000 Males >300 Females	Mortality ≥ 400 mg/kg Females (prelim) Mortality at 2000 mg/kg in 1 male. Weight loss, vasodilatation, diarrhoea, staining of the snout, soiling of the anogenital region, palpebral closure, lethargy, a hunched posture, chromodacryorrhoea, palpebral closure, dyspnoea and a wasted appearance GI macroscopic changes
1398/277	Rat/Crl:WI(G1x/ BRL/Han)BR	Preliminary: 50, 60, 75, or 100 Main: 60 IV	MLD: >60 mg/kg	Mortality ≥ 75 mg/kg Females Tachypnoea, lethargy, haematuria, salivation, palpebral closure, pilo-erection and rales, tremors, stained snout, chromodacryorrhoea, No deaths in main study at 60 mg/kg Tachypnoea; lethargy, lachrimation and palpebral closure within two hours of dosing and pilo-erection and stained snouts in females.

Repeat dose toxicity

Repeat-dose toxicity studies were performed in mice for up to 12 month, rats for up to 6 months, and cynomolgus monkeys for up to 12 months. The study design and major findings are summarised in table 7 below.

Table 7: Repeat-dose studies

Study ID	Species/Sex/ Number/Group	Dose/Route	Major findings
1398/262 14 days (QD)	Mouse 6/sex/group	0, 500, 1000, or 2000 Oral	Body weight and food consumption ↓ Group mean body weight gain for all M groups. ↓ food consumption in week 1 Haematology:↓ neutrophil count Clin. Chem: ↓ AST/ALT ≥ 1000 mg/kg M, 2000 mg/kg F. Increased protein, globulin, albumin (F) ≥1000 mg/kg. ↓ A/G ratio Macroscopic: Distension, thickening, irregular surface and raised foci in the stomach at all doses. **NOAEL considered 500 mg/kg**; **AUC_{24h} < 146,245 and < 158,868 ng•h/mL for M and F**
1398/289 28 days (QD)	Mouse 12/sex/group	0, 250, 600, or 1500 Oral	Mortality: 2 F at 1500 mg/kg due to arteritis, 1 F at 600 mg/kg and 1 M at 1500 mg/kg, undetermined No effects ophthalmology Clinical signs: swollen abdomen, hunched appearance, thinness in F ≥ 600 mg/kg, rapid respiration at 1500 mg/kg Body weight and food consumption: ↓ body weight gain in 1500 mg/kg M, ↓consumption in 1500 mg/kg F Haematology: ↑neutrophil count, ↓ lymphocyte count in M/F, ↑ white cell count in F Clin. Chem: ↑ globulin levels and total protein, slightly ↓ albumin and A/G ratio. ↓ K^+ and bilirubin. Organ weight: ↑ Liver and spleen weights in M/F Macroscopic: Large liver (1500 mg/kg F), spleen (F), thick pale stomach (≥ 600 mg/kg) Microscopic: Arteritis in multiple organs – inflamm cell infiltrates, perivascular edema/haemorrhage, necrosis, fibrosis, cardiac cartilaginous metaplasia. Lung perivascular inflammatory cell infiltration. Inflammatory lesions in the lung related to arteritis. Centrilobular hypertrophy in liver. Hyperkeratosis noted in the forestomach, with keratin layer thickening, gastritis.

			Synovitis stifle joint of 2M/1F. ↑ lymphoid hyperplasia Toxicokinetics: ↑ exposure on d28 v d1, and in F v M **No NOAEL due to findings at 250 mg/kg; AUC_{24h} values at this dose were < 101,173 and < 117,865 ng•h/mL for M/F**
1398/297 28 days (QD)	Mouse 12/sex/group	0, 5, 25, 75, or 150 Oral	Mortality: 1M at 75 mg/kg euthanized due to skin lesions. Arteritis noted in aortic root at based of heart. No effects on ophthalmology, clinical signs, body weight, food consumption Haematology: ↓ lymphocyte count in M/F Clin. Chem: ↑ globulin levels and total protiein, ↓ albumin and A/G ratio in F. Organ weight: ↓ kidney weight in 150 mg/kg F Macroscopic: Thick stomach in one 150 mg/kg F Microscopic: Arteritis in multiple organs – inflamm cell infiltrates, perivascular edema/haemorrhage, necrosis, fibrosis – in kidney and thoracic organs (M) and aortic root (F). Lung perivascular inflammatory cell infiltration in ≥ 75 mg/kg M Stomach hyperkeratosis ≥ 75 mg/kg/day Toxicokinetics: less than dose prop ↑ exposure on d28 v d2. **NOEL for arteritis in females was 75 mg/kg/day, not established in males; AUC_{24h} 41374 ng.h/mL in F**
1398/333 4 weeks (QD)	Mouse 12/sex/group	0, 1, 2, or 4 Oral	No significant treatment-related effects on mortality ophthalmology, clinical signs, body weight, food consumption haematology, organ weight, macroscopic or microscopic findings. Clin. Chem: ↓ ALT/AST. **NOAEL was > 4 mg/kg/day; Day 28 AUC24h values of 3810 and 3992 ng.h/mL for males and females, respectively.**
1398/373 13 weeks (QD)	Mouse 12/sex/group	0, 2, 4, 8, or 16 Oral	No significant treatment-related effects on mortality ophthalmology, clinical signs, body weight, food consumption haematology, organ weight, macroscopic findings. Microscopic: minor treatment related findings in the heart, lung and thymus at 16 mg/kg/day. Minor arteritis at the root of the aorta in 1M/2F at 16 mg/kg/day, perivascular inflammatory cell infiltration in the lung of 1 F

			at 16 mg/kg/day. **NOAEL 8 mg/kg/day; AUC_{24h} 9608 and 8988 ng.h/mL for M/F respectively.**
CC-10004-TOX-002 (WIL-553002) 90 days (QD)	Mouse 10/sex/group	0, 100, 300, or 1000 Oral	No effects on mortality, clinical observations or macroscopic necropsy findings Body weight and food consumption: ↓ body weight gain in and food consumption M/F Haematology: ↑neutrophil count, ↓ lymphocyte count in M/F ≥ 300 mg/kg/day Clin. Chem: ↑ haptoglobin and CRP in M/F, ↑ globulin in M Organ weight: ↑ liver weight at 1000 mg/kg, ↑ thymus weight Microscopic: inflammation and/or degeneration of the heart around the aorta or aortic root. Lung inflammation in the perivascular or peribronchiolar region. Centrilobular hepatocellular hypertrophy in liver. Lymphoid depletion in thymus of a few males at 1000 mg/kg/day and in the spleen in 2M. Perivascular inflammation in the mesenteric area and pancreas in 1M. **NOAEL was 100 mg/kg/day; corresponding to Day 86 AUC24h values of 24,318 and 25,478 ng.h/mL for M/F, respectively**
CC-10004-TOX-004 (WIL-553003) 6 months (QD)	Mouse 15/sex/group	0, 10, 100, or 1000 Oral	Mortality: 4 mice ≥ 100 mg/kg/day due to vascular/ perivascular inflammation, necrosis or hepatic infarction No treatment-related ophthalmic findings. Body weight and food consumption: ↑ body weight and food consumption in F. Haematology: ↓WBC, large unstained cells, and lymphocytes, ↑neutrophils ≥ 100 mg/kg M. Clin. Chem: ↑ globulin levels and total protiein, ↓ albumin and A/G ratio in F. ↓ Cl^- in F. ↑ haptoglobin Organ weight: ↑ liver weight at 1000 mg/kg, ↑ testes weight ≥ 100 mg/kg M, ↑ brain heart and liver weight ≥ 10 mg/kg Macroscopic: No findings at scheduled necropsy Microscopic: Vascular and perivascular inflammation in the heart (aortic root and cardiac arteries), mesentery, and pancreas at ≥ 100 mg/kg/day. Vascular mineralization and cartilaginous metaplasia (aortic root) were occasionally associated with inflammatory changes in the heart at ≥ 100 mg/kg/day. Vascular/ perivascular inflammation of the liver and fibrosis around the bile ducts in

			males at 100 mg/kg/day. Inflammation and necrosis of the gall bladder in 1000 mg/kg/day F. Minimal centrilobular hepatocellular hypertrophy. ↓ early cystic endometrial hyperplasia in the uterus, considered incidental. Malignant lymphoma in multiple tissues was noted in 1 F, an alveolar/bronchiolar adenoma was present in the lung of 1 F, considered incidental. **NOAEL 10 mg/kg/day. AUC_{0-24hr} on Day 177 5614 and 5842 ng.mL/hr in M/F.**
CC-1000 4-TOX-0 03 (WIL-55 3001) 90 days (QD)	Rat 10/sex/group	0, 30, 100, 300, or 1000 (M) 0, 0.3, 3, 10, or 30 (F) Oral	Mortality: ≥ 30 mg/kg in M, ≥ 10 mg/kg in F, with overt toxicity, led to early termination of dosing in these groups. Body weight and food consumption: ↓ body weight gain ≥ 30 mg/kg M, 0.3 mg/kg F, ↓ food consumption at higher doses. Haematology: ↑ WBC, neutrophil, lymphocyte, monocyte count ≥100 mg/kg M, ≥3 mg/kg F. ↑ mean/absolute reticulocytes ≥ 10 mg/kg F. Clin chem.: ↑ globulin levels, ↓ albumin and A/G ratio in. ↑ haptoglobin in F at week 0. Organ weights: ↓ thymus weights ≥30 mg/kg M/F Macroscopic: Euthanized animals enlargement or dark red discoloration of the adrenal glands, dark red or yellow contents, dark red discoloration, distention or intussusception of the intestinal tract, enlargement of the lymph nodes, white areas in the mesentery, enlargement, gray discoloration or pallor of the salivary glands, small or pallor of the spleen, distention or dark red areas in the stomach, and small or edema of the thymus. Microscopic: Mesentery (inflammation, fibroplasia/fibrosis, adipose tissue atrophy, and vascular degeneration, hemorrhage, and inflammation), heart (perivascular and epicardial inflammation), stomach and/or intestine (mucosal inflammation, hemorrhage, congestion, erosion and ulceration), lymphoid tissues (lymphoid depletion and/or necrosis and neutrophilic inflammation), adrenals (cortical hypertrophy and/or hyperplasia and hemorrhage), bone marrow (hypocellularity and/or erythroid depletion and hemorrhage), salivary gland (acinar atrophy and excessive

			mucous production), and esophagus (hyperkeratosis). Isolated diffuse hepatocellular atrophy in M Only thymus/spleen unresolved at recovery Toxicokinetics: Greater exposure in F v M, no accumulation. **No NOAELs determined. MTD 30 and 3 mg/kg/day in M/F; Day 88 AUC_{24h} values of 1281 and 6984 ng•h/mL respectively.**
1398/283 Repeat dose: 14 days (QD)	Cynomolgus monkey 2/sex/group	MTD: 0, 100, 300, 650, or 1000 Repeat dose: 750	No mortality, clinical signs included vomiting Body weight and food consumption: ↓ body weight at 750 mg/kg/day Haematology: ↓ RBC, Hb and packed cell volume, ↑ neutrophils and lymphocytes. Clin chem.: ↑ plasma globulin Macroscopic: ↓ thymus size, tail lesions (M). Microscopic: thymic atrophy correlated w/ macroscopy, mesenteric/mandibular lymph node and spleen atrophy. ↑ haemopoiesis in sterna marrow. Minor pyaemic foci in the heart and lung, arteritis in one section of epididymis and minor lymphadenitis in the mandibular lymph node. **No NOAEL, MTD 750 mg/kg/day**
CC-1000 4-TOX-0 10 (1398-4 91) Phase I: 14 days (BID or QD) Phase II: once	Cynomolgus monkey 3 F/group	0, 50, or 250 (BID) and 200, 200, or 1000 (QD) 200 (QD) Oral	No mortality, clinical signs included vomiting Body weight and food consumption: decreased body weight in some animals led to increased food supplementation. Haematology: minor ↓ RBC, Hb. Clin chem.: No treatment-related effects Organ weight: No treatment-related effects Macroscpoic: discolored mucosa in the fundus or pylorus region of stomach. Microscopic: multifocal moderate degeneration /necrosis of the myocardium accompanied by a minimal subacute myocardial inflammation, moderate hemorrhage and/or moderate hemorrhage (200 and 1000 mg/kg daily) **NOAEL 50 mg/kg BID**
1398/296 28 days (QD)	Cynomolgus monkey 3/sex/group	0, 50, 180, or 650 Oral	No mortality; clinical signs included reflux, vomiting up to 3h post dose ≥ 180 mg/kg/day, salivation in 1M/F No effects on body weight, ophthalmoscopy, ECG, clinical chemistry. Haematology: ↑ neutrophil levels, ↑ erythroblasts in Males with uncertain

			relevance. Organ weights: ↑ liver weight in M at 650 mg/kg/day Microscopic: vascular wall degeneration/necrosis with formation of small thrombi, perivascular oedema and minor inflammatory cell infiltration consisting predominantly of polymorphs and eosinophils. **NOAEL ≥ 650 mg/kg/day; Day 28 AUC_{24h} values of 78,989 and 58,271 ng.h/mL for M and F.**
1398/368 13 weeks (QD)	Cynomolgus monkey	0, 25, 85, or 300 Oral	No mortality, isolated vomiting/retching No effects on body weight, ophthalmoscopy, ECG, clinical chemistry, haematology, clinical chemistry, organ weights, or macroscopic findings. Microscopic: small increase in hepatocyte vacuolation incidence/severity. **NOAEL 300 mg/kg; AUC_{24h} values of ≥ 32,523 and ≥ 23,307 ng.h/mL**
CC-10004-TOX-005 (WIL-553004) 12 months (QD)	Cynomolgus monkey	0, 60, 180, or 600 Oral	Mortality: 1F euthanized, not treatment related Clinical signs: ↑ red vaginal discharge incidence Body weight and food consumption: Observed inappetance without body weight changes. Haematology: ↑ neutrophil levels, ↑ lymphocytes. ↑ fibrinogen at 600 mg/kg M, ≥ 180 mg/kg F. ↓ mature T cells and NK cells in M Clin chem.: ↓ glucose, ↓ albumin, variable ↑ CRP and haptoglobin. No effects on ophthalmology, ECG, organ weights, macroscopic findings. Microscopic: Small chronic inflammation foci in heart, liver, kidneys, nasal cavity; not treatment related. **NOAEL 600 mg/kg/day, AUC_{24h} values of 42,608 ng.h/mL and 26,936 ng.h/mL in M/F. M3 and M12 metabolites were 2768/1065 ng.h/mL and 90,035/63,662 ng.h/mL in M/F**

Toxicokinetics

The toxicokinetic parameters in mouse, rat, and cynomolgus monkey repeat dose studies are summarised in table 8 below.

Table 8: Toxicokinetic parameters in mouse, rat, and cynomolgus monkey repeat dose studies

Study ID	Daily Dose (mg/kg)	Steady state AUC_{24h} (ng.h/ml)		Animal:Human Exposure Multiple	
		♂	♀	♂	♀
CD-1 mouse					
1398/262	500	146245	158868	20.0	21.7
Day 14	1000	174239	186415	23.8	25.5
	2000	215866	222283	29.5	30.4
1398/289	250	101173	117865	13.8	16.1
Day 28	600	162965	194262	22.3	26.6
	1500	205842	279734	28.2	38.3
1398/333	1	842	882	0.1	0.1
Day 28	2	2176	1376	0.3	0.2
	4	3810	3992	0.5	0.5
1398/297	5	6327	6254	0.9	0.9
Day 28	25	16207	17109	2.2	2.3
	75	54158	41374	7.4	5.7
	150	65576	66846	9.0	9.1
1398/373	2	2143	2418	0.3	0.3
Week 13	4	4069	4764	0.6	0.7
	8	9608	8988	1.3	1.2
	16	15960	14895	2.2	2.0
CC-10004-TOX-002	100	24318	25478	3.3	3.5
	300	52419	54890	7.2	7.5
Day 86	1000	80724	87828	11.0	12.0
CC-10004-TOX-004	10	5614	5842	0.8	0.8
	100	21289	32491	2.9	4.4
Day 177	1000	72183	76010	9.8	12
CC-10004-TOX-1125	1	585	789	0.1	0.1
	4	2110	2990	0.3	0.4
PND21	10	5270	2830	0.7	0.4
SD rat					
C-10004-TOX-003	30/0.3	1281	592	0.2	0.1
	100/3	NA	6984	NA	1.0
Day 88	300/10	NA	NA	NA	NA
	1000/30	NA	NA	NA	NA
Cynomolgus monkey					
1398/283 Day 14	750	123597	116035	16.9	15.9
CC-10004-TOX-010	100		33754		4.6
	200		67853		9.3
Day 14	200	NA	44506	NA	6.1
	500		93755		12.8
	1000		92975		12.7
1398/296	50	15079	9666	2.1	1.3
Day 28	180	52893	34772	7.2	4.8
	650	78989	58271	10.8	8.0
1398/368	25	13254	12461	1.8	1.7
Week 13	85	12592	20293	1.7	2.8
	300	32523	23307	4.5	3.2
CC-10004-TOX-005	60	16443	17526	2.3	2.4
	180	23841	22561	3.3	3.1
Day 358	600	42608	26936	5.8	3.7

NOAEL Dose; where determined.

The comparison of Ampremilast metabolites M3 and M12 in Mouse, Monkey, and Human is described in table 9 below.

Table 9: Comparison of Ampremilast metabolites M3 and M12 in Mouse, Monkey, and Human

	Metabolite M3 (Male/Female)		Metabolite M12 (Male/Female)	
	AUC	**Ratio to human**	**AUC**	**Ratio to human**
Human	Trace	NA	3930d	NA
6-month Mouse	5.29/15.2	NC	1459/1856	0.37/0.47
12-month Monkey	2768/1065	NC	90035/63662	23/16

AUC = area under the plasma concentration-time curve; NA = not applicable; NC = not calculated. All data are presented as AUC24h (ng•h/mL)

Genotoxicity

Table 10: Overview of genotoxicity studies

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria GLP	Salmonella strains TA98, TA100, TA1535, TA1537 and TA102	Up to 5000 µg/plate +/- S9	Cytotoxicity at ≥2500 in TA98, TA1537 Negative +/- S9
Chromosomal aberrations in mammalian cells GLP	Human peripheral blood lymphocytes	Up to 448 µg/mL - S9 Up to 700 µg/ml + S9	No increase in chromosomal aberrations +/- S9
Chromosomal aberrations in vivo GLP	Mouse, micronuclei in bone marrow	0, 500, 1000, 2000 mg/kg/day	No increase in micronuclei formation up to 2000 mg/kg/day

Carcinogenicity

GLP-compliant 104-week oral carcinogenicity studies were performed in mice and rats

Long-term studies

Table 11: Summary of carcinogenicity studies in mouse and rat

Study ID /GLP	Dose/Route (mg/kg/day)	AUC_{24h} (d175)	Species/No. animals	Major findings
CC-10004-TOX-006	100, 300 (200), and 1000 (500 F) Oral	Male: 32419 45397 *52856* Female 37655 47305 *75049*	Mice 70/sex/group	**No treatment-related neoplastic changes up to 1000/500 mg/kg/day.** Incidence of malignant lymphoma, skin sarcoma in line with historical ctls Mortality: deaths due to vascular degeneration/inflammation-related hemorrhage. General trend in ↓ survival in M. No effects on clinical signs, incidence of palpable masses, Body weight & food consumption: ↑ b.w. and f.c in F. ↑ bw in M at w13 but ↓ at w32-73. Haematology: ↑ neutrophil, ↓ RBC mass and lymphocyte count, ↑ reticulocyte counts Clin chem.: ↑ total protein and globulin, blood urea nitrogen, ↓ Alk Phosphatase

				Macroscopic: distended gall bladder in M/F, Harderian gland discolouration in F Microscopic: Heart: Fibrosis of epicardium, coronary vasculitis, proliferation of spindle cells and thickening of the vessel wall. Skeletal muscle: hemorrhage Lungs: perivascular and/or peribronchiolar lymphocyte and plasma cell infiltrates Vagina: ↑ mucification
CC-10004-TOX-007	3, 10, 20 M 0.3, 1, 3 F	Male: 289 537 *608* Female: 529 1814 *7721*	SD rats 70/sex/group	**No treatment-related neoplastic changes up to 20 or 3 mg/kg/day in M/F.** Mortality: deaths due to GI inflammation/necrosis ≥ 3 mg/kg M, ≥ 1 mg/kg F. General trend in ↓ survival in M. No effects on clinical signs, incidence of palpable masses Body weight & food consumption: ↓ bw in M Haematology: ↑ neutrophil, WBC, lymphocytes. ↓ RBC mass, ↑ reticulocyte counts Clin chem.: ↑ globulin, ↓ albumin Macroscopic: GI findings at euthanasia Microscopic: gastrointestinal tract: inflammation, erosion and ulceration goblet cell hyperplasia heart: necrosis and fibroplasias lymphoid tissue: acute inflammation and hyperplasia liver: vasculitis, adrenal cortex: necrosis bone: periosteal hyperostosis skeletal muscle: degeneration and mineralization vagina/cervix: epithelial mucification

Reproduction Toxicity

The mouse and monkey were selected as the rodent and non-rodent species for the embryo-fetal development evaluation. The monkey was selected due to a lack of measurable exposure to apremilast in rabbits after oral administration. The mouse was used as the species to assess fertility and mating and pre- and postnatal development based on the pharmacokinetic and metabolic profile which is more similar to humans.

Fertility and early embryonic development

Table 12: Summary of fertility and early embryonic development studies

Study type / Study ID / GLP	Species; No. / sex / group	Route & dose mg / kg / day	Dosing period	Major findings
Fertility				
CC-10004-TOX-001 GLP	Mouse 25 M/F	0, 100, 300, 1000 Oral	M: 28 days pre-cohab F: 15 days pre-cohab to GD7	No mortalities, clinical or necropsy findings attributed to apremilast. Body weight: ↑ b.w. gain in 1000 mg/kg/day M, ≥100 mg/kg/day F, but ↓ after cessation. ↑ Gestation b.w. Mating/Fertilty: ↑ #days cohab ≥300 mg/kg/day, ↓ Fertility Index, ↓ mating mice. No effects on estrous cycle. No effects on sperm parameters ↑ post-implant losses and unviable embryos at 1000 mg/kg Organ weight: ↑ heart weight in M, testes weight, ↓ seminal vesicles, prostate. **No NOAEL was established**
CC-10004-TOX-011 GLP	Mouse 25 M/group	0, 1, 10, 25, 50 Oral	70 days pre-cohab → mating	No apremilast-related deaths, or clinical or necropsy observations parameters Body Weights: ↑ ≥ 10 mg/kg Mating/Fertility: No effects on mating, fertility, or sperm parameters. Organ weight: ↑ testes absolute weight and b.w. ratio ≤25 mg/kg **NOAEL 50 mg/kg/day; Day 70 AUC_{24h} of 21,040 ng.h/mL**
Fertility and EED				
CC-10004-TOX-012 GLP	Mouse 25 F/group	0, 10 20, 40, 80 Oral	15 days pre-cohab to GD15	No apremilast-related mortality or clinical signs. Female mating and fertility indices not affected by treatment. Body Weights: ↓ b.w. gain ≥ 40 mg/kg Mating/Fertility: ↓ number of estrous cycles, ↑ extended cycles at 20 & 80 mg/kg/day. ↑ #days cohab ≥20 mg/kg/day ↑ post-implant losses, total/early resorption ≥ 20 mg/kg/day, ↓ litter sizes, number of live fetuses and fetal b.w at ≥40 mg/kg ↓ ossified tarsals ≥ 20 mg/kg/day, ↑ incompletely ossified supraoccipitals at ≥40 mg/kg /day.

				Organ weight: ↑ heart weight ≥20 mg/kg **NOEL for female fertility, maternal & developmental NOAEL was 10 mg/kg/day; AUC24h of 29,215 ng.h/mL**

Embryo-fœtal development

Table 13: Summary of Embryo-fœtal development studies

Study type/ Study ID / GLP	Species; No./sex/ group	Route & dose mg/kg/day	Dosing period	Major findings
Embryo-fœtal development				
1398/308 GLP *Range Finding*	Mouse	0, 250, 500, or 750 Oral	GD 6-15	Slight maternal toxicity (decreased weight gain, food intake and gravid uterus weight) at 500 and 750 mg/kg/day. No embryo-fetal toxicity or external defects up to 750 mg/kg/day.
1398/309 GLP	Mouse 24 F/group	0, 250, 500, 750 Oral	GD 6-15	Mortality: 1 F euthanised with pallor, sluggish behavior, labored respiration, red discharge from urogenital region, semi-closed eyes and sore/lesion on neck, distended gall bladder, stomach Body Weights: ↓ b.w. gain & food consumption ≥ 250 mg/kg Organ weight: ↓ gravid uterus weight in treated groups EFD: Pregnancy rate unaffected, ↑ embryo-fetal loss, ↑ intrauterine deaths & post-implantation losses. ↓ Litter weight and fetal weight at all doses, ↓ placental weight ≥ 500 mg/kg/day. ↑ rate incomplete ossification and/or sternabrae development **No NOAEL determined** **Teratogenicity NOAEL 750 mg/kg (highest dose tested)**
CC-10004-TOX-009 non-GLP Range Finding	Rabbit	Initial phase: 0, 5, 50 Extended phase: 0, 15 Oral	1 day	Initial phase: 50 mg/kg – All rabbits terminated on Day 2 due to severe toxicity including decreased motor activity, hyperpnea, twitches, perivaginal discharge. Abnormal feces, perivaginal discharge or red/dark brown urine. Weight loss &

				reduced food consumption. Macroscopic findings (on Day 5) included dark brown or black kidneys, discolored fluid in urinary bladder, pale heart or distended stomach or colon. Extended phase: Scant feces in controls. Decreased motor activity, hyperpnea, ataxia, red perinasal and perioral substance, urine-stained fur at 15 mg/kg. All rabbits lost weight and had reduced food consumption, and had no macroscopic necropsy findings (on Day 2). Due to the toxicity of formulation, the EFD portion of the study was not conducted.
1398/290 GLP *Range Finding*	Rabbit	0, 250, 500, 1000 Oral	13 days	No effects on clinical signs, body weights, food intake, or macroscopic necropsy findings up to 1000 mg/kg/day.
1398/291-D6154 GLP *Range Finding*	Rabbit	0, 250, 500, 1000 Oral	GD 7-19	No maternal or embryo-fetal developmental toxicity up to 1000 mg/kg/day. A subsequent study (Report 1398/292) demonstrated a lack of measurable exposure of apremilast in rabbits.
1398/292 GLP	Rabbit 34 F/group	0, 250, 500, 1000 Oral	GD 7-19	1 F at 1000 mg/k/day aborted on DG27 Body Weights: ↓ b.w. gain GD19-24, ↓ food consumption GD 19-23 EFD: Slight ↓ placental weight, F fetal weight, not significant. No treatment-related effects on uterine weight, or fetal external, visceral or skeletal development abnormalities. **NOAEL 1000 mg/kg/day; There was no apremilast exposure detected in maternal plasma**
CC-10004-TOX-013 GLP	Monkey 18F/group	0, 20, 50, 200, 1000 Oral	GD 20-50	No mortality, no macroscopic findings. Clinical signs included emesis, salivation, other signs attributed to process of abortion Maternal body weight: ↓ bw in animals that aborted EFD: Dose-dependent ↑ in embryo/fetal loss. External fetal findings not considered treatment related due to absence of dose response. Ossifaction or misaligned vertebrae, used ribs, scoliosis, all considered not

				related to treatment. **Maternal NOAEL 20 mg/kg/day; GD 50 AUC of 10,100 ng./mL** **EFD NOAEL 1000 mg/kg/day; GD 50 AUC of 62,400 ng.h/mL**

Prenatal and postnatal development, including maternal function

Table 14: Summary of PPND studies

Study type/ Study ID / GLP	Species; No./sex/ group	Route & dose mg/kg/day	Dosing period	Major findings
Peri & postnatal development				
CC-10004-TOX-1 139 GLP	Mouse 25/group	0, 10, 80, 300 Oral	GD6-DL 20	F0 Mortality: One 300 mg/kg/day mouse died, Clinical signs of red perivaginal substance, hyperpnea, and a clonic convulsion. Other deaths not treatment related. Clinical signs: pale ears, hunched posture, dehydration, clonic convulsion at 300 mg/kg/day. Hypernea at 80 and 300 mg/kg. Body weight: ↓ maternal b.w. on DL 4 & 14, ↓ b.w. gain GD 12-18, DL 1-14 at 300 mg/kg/day. PPN: ↑ stillborn pups at ≥ 80 mg/kg/day and dams with no surviving pups (300 mg/kg/day) ↓ Litter sizes and average litter weight, and pup weight ≥ 80 mg/kg/day ↑ pups found dead, sacrificed due to adverse signs or missing and presumed cannibalize ≥ 80 mg/kg/day F1 necropsy: Increased milk in stomach of pups ≥ 80 mg/kg F1: No treatment-related effects on clinical signs, body weights, sexual maturation, passive avoidance, motor activity, mating, fertility, or c-section parameters **Maternal NOAEL 10 mg/kg/day, F1 generation 10 mg/kg/day** **No TK measurements**

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Two-Week Oral (Gavage) Dosage Range Finding Repeated-Dose Toxicity Study of apremilast in Neonatal Mice (Non-GLP)

Apremilast was administered by oral gavage to neonatal male and female mice (8/sex/group) at 0, 10, 100, and 1000 mg/kg/day on Days 7 through 20 postpartum (DPs 7 through 20). Mortality occurred in all pups at 1000 mg/kg/day, 7 out of 8 pups per sex in the 100 mg/kg/day group, and 2 male pups in the 10 mg/kg/day group. Clinical observations included increased incidence of dehydration at ≥10 mg/kg, thin body condition (≥10 mg/kg/day females and 100 mg/kg/day males), and cold bodies and decreased motor activity at ≥100 mg/kg/day. Consistent body weight loss prior to death occurred in the 1000 mg/kg/day group. The surviving pups in the 100 mg/kg/day dosage group tended to gain weight after DP 10. Body weight gain in the 10 mg/kg/day dosage group was reduced after the first two dosages (DPs 7 to 8 and 8 to 9) and then generally comparable to control group values after DP 10. Average body weights on DP 21 were 8% and 46% below control and 17% and 43% below control for males and females in the 10 and 100 mg/kg/day dosage groups, respectively. There were no test article-related macroscopic findings.

Dose-limiting toxicity was clearly established at 100 and 1000 mg/kg/day based on mortality on DP 9-12.

Thirteen-Week Oral (Gavage) Repeated-Dose Toxicity and Toxicokinetic Study of Apremilast in Juvenile Mice (GLP)

Apremilast was administered orally (via gavage) to juvenile male and female mice (30/group) at dosage levels of 0 (1% w/v aqueous CMC), 1, 4, and 10 mg/kg/day on postnatal days (PNDs) 7 through 97. Totals of 6, 6, 9 and 17 mice in the 0, 1, 4 and 10 mg/kg/day dosage groups, respectively, were found dead, missing, or sacrificed due to adverse signs during the dosage period, predominantly over the first week of dosing. At 4 mg/kg/day, 5 of 9 deaths were attributed to traumatic injury and 3 were missing and presumed cannibalized.

Apremilast was associated with mild/moderate dehydration in females at ≥4 mg/kg/day and males at 10 mg/kg/day. Decreased activity was also seen in females at ≥10 mg/kg/day. Body weights were generally decreased with apremilast at ≥ 4 mg/kg/day from PND 7 to 14 but a compensatory increase in body weight gain was seen from PND 22 onwards, and the changes were not considered adverse.

Sexual maturation was slightly delayed for male and female pups in the 10 mg/kg/day dosage group and the average day on which preputial separation occurred was significantly increased in this group. Delays were within historical controls and were related to body weight gain and therefore not considered adverse. Clinical pathology revealed increased lymphocytes in females at ≥4 mg/kg/day of up to 1.8 fold at the end of the dosing phase.

There were no apremilast-related effects on motor activity, functional observational battery, Morris water maze performance, mating, fertility or Caesarean-sectioning parameters, femur lengths, organ weights, necropsy, or histopathological observations.

Generally, administration of apremilast was considered to be well tolerated in male and female juvenile mice. The NOAEL was considered to be 10 and 4 mg/kg/day in males and females respectively, corresponding to AUCs of 7470 and 2990 ng•hr/mL on PNDs 7 and 21, respectively for females, and 13600 and 5270 ng•hr/mL on PNDs 7 and 21, respectively, for males.

Local Tolerance

Dermal Irritation

Acute Dermal Irritation Study in Rabbits of CC-10004 in Ethanol:Propylene Glycol (non-GLP)

Apremilast was evaluated for its potential dermal irritation and/or corrosive effects by dermal application to 3 New Zealand White rabbits at a concentration of 0.3 mg/mL in ethanol:propylene glycol (40:60 %v/v) (Report CC-10004-TOX-500). Hair on the dorsal trunk of the rabbits was removed and 0.5 mL of the test article was applied and held on the skin for 4 hours. The test site was scored for erythema/eschar formation and edema within 30 to 60 minutes and at 24 and 48 hours following patch removal. All animals survived to study termination and there was no effect on body weights. There was no observed erthema/eschar or edema formation; therefore, apremilast was classified as a non-irritant.

Skin Sensitization Study (Buehler Method) in Guinea Pigs of CC-10004 in Ethanol:Propylene Glycol (non-GLP)

A total of 2 males and 2 females were assigned to the range-finding phase, and the test article was administered to 4 dose sites on shaved dorsal trunk/scapular region of each animal at dose levels of 0 (ethanol:propylene glycol; 40:60 %v/v), 0.05, 0.5, and 3.0 mg/mL (Report CC-10004-TOX-501). Closed topical patches were applied as 0.4 mL liquid. No signs of irritation were observed at 24 and 48 hours after dose application; therefore, a concentration of 3.0 mg/mL was selected for the definitive skin sensitization phase of the study.

In the definitive skin sensitization study, guinea pigs were assigned to apremilast (10/sex), vehicle control (5/sex) or hexylcinnamic aldehyde (HCA; positive control; 5/sex) groups. During the induction phase, animals in the apremilast or positive control groups received topical patch applications (0.4 mL) of their respective drugs for 6 hours once weekly for 3 weeks. The challenge phase occurred 2 weeks after the last induction application. The test or vehicle control article was applied topically to the animals in the vehicle control and the apremilast groups, and the HCA was given similarly to the positive control animals. The application sites were scored at 24 and 48 hours after the challenge application.

No signs of irritation were observed in any of the animals in the apremilast groups. No animals in the vehicle control group had positive signs of irritation but 3 animals had equivocal signs of irritation. The positive control group also responded in an equivocal manner. Based on these equivocal results, the apremilast and positive control animals were rechallenged along with a group of previously untreated control animals.

In the rechallenge phase, positive signs of irritation were observed in 1 of 20 animals in the apremilast group at 48 hours scoring. This resulted in a sensitization index of 5% (weak sensitizer). No signs of irritation were observed in the vehicle control group. The positive control group responded in an appropriate manner, with 70% of the animals observed with erythema scores of 1 or greater (strong sensitizer).

Immunotoxicity

No specific immunotoxicity studies were conducted with apremilast. In the single- and multiple-dose general toxicity studies in mice, rats and monkeys, effects of apremilast on the immune system were largely limited to inflammatory changes associated with vasculitis in rodents. This pro-inflammatory effect observed in rodents is a known class effect of PDE4 inhibitors and is considered less relevant to humans. In contrast, studies in monkeys revealed no convincing microscopic evidence of apremilast-related tissue inflammation. No consistent hematological evidence of inflammation was seen. Although neutrophilia and lymphopenia were cited in some monkey studies, including the 12-month chronic study, these changes were negligible in magnitude and/or within the range of pretest values. No toxicologically-significant changes in inflammatory markers were seen in the blood of monkeys dosed with apremilast on any study.

Aside from the rodent-predominant pro-inflammatory changes, there is little evidence from standard toxicity studies for immunotoxic potential of apremilast. Although mildly decreased peripheral blood lymphocytes and lymphoid atrophy/depletion in lymph nodes, spleen and/or thymus were seen in rodents administered apremilast, these findings were associated with inflammatory lesions and are consistent with normal physiologic responses of lymphocytes to inflammation and stress, rather than a direct lymphotoxic effect of the drug. In monkeys, alterations in lymphoid parameters were far lower in incidence and severity, and definitive apremilast-related inflammatory lesions were not observed. Lymphoid atrophy was seen in monkeys only at the highest dose tested (750 mg/kg) after 2 weeks. No evidence of effects on either lymphoid organ weights or histology was seen at doses up to 650 mg/kg and for study durations as long as 12 months. Although decreased peripheral lymphocytes were cited in the 12-month monkey study, effects were minimal and not considered toxicologically meaningful or associated with lymphoid atrophy in tissues. Immunophenotyping was conducted during this study and revealed no definitive apremilast-related effects. A statistically significant effect on T cells and NK cells was observed in males during Week 13; however, significance was no longer evident by Week 51 and a similar change was not seen in females, thus a causative relationship of this minor effect to apremilast administration could not be made.

There were no increased incidences of opportunistic infections or tumours in any of the completed toxicology studies. In clinical studies, vasculitis has not been associated with apremilast treatment. There were no notable changes in clinical laboratory tests or peripheral blood markers of inflammation monitored in the Phase II clinical studies.

Metabolites

In vivo, apremilast is converted to several metabolic products, including the hydrolysis degradants M1 and M2, the *O*-desmethyl metabolite M3 (tested racemate CC-15604 and S isomer CC-16085, respectively), the *O*-desethyl metabolite M5, the *N*-deacetyl metabolite M7, the *O*-desmethyl glucuronidated metabolite M12, the *N*-deacetylated-*O*-desmethylated glucuronide M14, the acetamide-hydroxy-glucuronide M16, and the acetamide-hydroxy metabolite M17. The synthesized metabolites, including M12 isolated from human urine, were assayed for PDE4 enzyme and TNF-α production inhibitory activities and compared to the parent drug (Report 5275-179; Report 5347-137; Report 5424-75; Report 5638-96). Only the M7 and M17 metabolites (represented as CC-10055 and CC-16401) demonstrated potent inhibition of both PDE4 enzyme activity and TNF-α production, indicative of pharmacologically active apremilast metabolites. These data showed that the major circulating and excreted metabolites of apremilast are inactive or markedly less active towards the PDE4 enzyme and TNF-α production. The two pharmacologically active apremilast metabolites, M7 and M17, account for less than 1% of the circulating radioactivity in humans and are not anticipated to contribute to the pharmacodynamic effects to a notable extent. Based on the observation that *O*-demethylation is a major metabolic pathway in human, levels of M3 and M12 were measured in the chronic mouse and monkey studies.

Studies on impurities

The only specified impurities for the apremilast drug substance (DS) and drug product (DP) are RC6 and RC8. RC6 is also a minor metabolite (M7) in humans and animals, and it was present in the batches used for a number of the pivotal toxicology studies, including the 26-week mouse, 52-week monkey, and the mouse and rat carcinogenicity studies.

An in silico evaluation using the quantitative structure-activity relationship (QSAR) genotoxicity predictive tools showed that there was no potential genotoxic structural alert for RC8; however, the RC6 impurity contains a structural alert for potential mutagenicity. Therefore, RC6 was evaluated for its mutagenic potential in an in vitro bacterial reverse mutation assay described below (Report CC-10004-TOX-015) and the results of the assay were negative. Per ICH Q3A Guidance (2002), the levels of these impurities are set to be below the qualification threshold of 0.15%.

The mutagenic potential of apremilast spiked with 5% w/w CC-10055 (RC6 impurity of apremilast) was investigated in a bacterial reverse mutation assay using 4 *Salmonella typhimurium* tester strains (TA98, TA100, TA1535 and TA1537) and *Escherichia coli* strain WP2 *uvr*A in the presence and absence of Aroclor-induced rat liver (S9) at 1.5 to 5000 µg/plate apremilast with 5.5% RC6 impurity (250 µg RC6 at maximum concentration). No positive response was seen at up to 5000 µg/plate, but precipitate was seen at 5000 µg/plate. Under the conditions of this study, apremilast spiked with 5% w/w CC-10055 was concluded to be negative in the bacterial reverse mutation assay with all of the tester strains in the absence and presence of S9.

Other studies

Oral (Gavage Administration) Comparative Toxicity Study of Apreimilast R and S enantiomers in the Female Rat

A study of the relative toxicity of the apremilast (S enantiomer) and CC-10007, its R enantiomer, in the female rat at an oral dose of 50 mg/kg/day indicated marked differences in. CC-10007 is 8-fold less potent than CC-10004 for PDE4 enzyme inhibition, with an IC_{50} of 0.611 µM (Report 5042-107). Following the 14 days of dosing, there was no indication of adverse effects with CC-10007; therefore, surviving animals in that group were dosed for an additional 16 days for a total of 30 days. All animals given apremilast were euthanized on Day 3 after only 2 doses following marked weight loss and reduction in food consumption, and poor general condition. Macroscopic examination was not performed on these animals at necropsy. In the CC-10007 group, one rat was terminated on Day 10 due to poor condition of swollen abdomen, pallor and staining of the urogenital region; macroscopic examination was not performed. Swollen abdomen was also observed in 7 out of 9 surviving animals in this group; this was first observed on Day 11 but was no longer present by Day 17. There were no CC-10007 effects on body weight, food consumption or macroscopic necropsy findings in the surviving animals. Limited toxicokinetic sampling showed that each enantiomer was systemically absorbed following its oral administration to female rats.

Evaluation of Biomarkers for Predicting Toxicity of Apremilast in Rat

The objective of this study was to develop a biomarker profile over time that could be used to follow the development and recovery of toxicity induced by apremilast in rats. Female rats (25/group) were dosed orally at a dose volume of 5 ml/kg with vehicle or 10 mg/kg/day of apremilast for 7 consecutive days followed by an 11-day recovery period. On Days 3, 6, 8 (recovery day 1), 14, and 18, five animals each from the apremilast and vehicle-treated groups were euthanized and blood, tissue and peritioneal lavage samples were collected for analysis. Results were consistent with the 90 day repeat dose toxicity study in rats, with GI clinical signs, hypoactivity, body weight loss, haematology and serum chemistry changes, and histopathological changes in mesentery thymus and small intestine.

Plasma biomarkers that correlated with the onset of the inflammation included an increase in fibrinogen, CRP, lipase, vascular endothelial growth factor (VEGF), monocyte chemoattractant protein (MCP)-3 and macrophage colony stimulating factor (MCSF) and decreases in leptin, MDC, and von Willebrand Factor (vWF). In addition, a significant increase in neutrophils and changes in biomarkers (increases in

fibrinogen, haptoglobin, VEGF, IgA, vWF, IL-11, and MCP-1 and decreases in leptin and RANTES [also known as chemokine ligand 5]) were observed in the peritoneal lavage samples of apremilast-treated rats.

Oral Toxicity Study in Mice to Investigate the Time Course for Development and Recovery of Inflammatory Lesions in Multiple Tissues

Apremilast was administered via oral gavage to female mice (36/group) once daily 1000 mg/kg/day for either 90 days, or 300 and 100 mg/kg/day for 14 days with a further 31 day or 76 day recovery period.

Five animals (2 at 300 mg/kg/day and 3 at 1000 mg/kg/day) died or were euthanized in extremis before their scheduled necropsies. Macroscopic and microscopic evaluations revealed the possible cause of death as gavage trauma for 2 animals and stress for 1 animal; no specific causes were evident in the remaining 2 early mortalities. Deaths were not considered treatment-related.

Body weights were increased prior to recovery at d13, and persisted in animals treated for 90 days. Higher globulin and urea nitrogen levels and lower A/G ratio were noted in all apremilast-treated groups at day 14. There were no clinical observations or haematology findings. Histological lesions were observed in the thymus and mesenteric lymph nodes (300 and 1000 mg/kg/day) and liver (1000 mg/kg/day). Thymic lesions reversed following 31-day recovery. All changes in mesenteric lymph nodes were resolved on Day 90 regardless of continued dosing or a 76-day recovery period. At 1000 mg/kg/day, liver lesions (hepatocellular hypertrophy) were observed with continuous dosing for 3, 14 and 45 days; complete recovery occurred by Day 90 with continued treatment or a 76-day recovery period.

Photoxicity study - Neutral Red Uptake Phototoxicity Assay of CC-10004 in Balb/c 3T3 Mouse Fibroblasts

Apremilast was evaluated for its phototoxicity potential by measuring the relative reduction in viability of Balb/c 3T3 mouse fibroblasts exposed to apremilast and ultraviolet radiation (+UVR), as compared with the viability of fibroblasts exposed to apremilast in the absence of ultraviolet radiation (-UVR). Results from this study showed that apremilast, at up to 101.8 mg/L, the highest achievable concentration in 1% DMSO in DPBS, demonstrated no cytotoxic effect (absence of UVR exposure) or phototoxic effect (with UVR exposure) in the assay by either the Photo Inhibition Factor or Mean Phototoxic Effect criteria.

2.3.5. Ecotoxicity / environmental risk assessment

Apremilast is currently being developed for use in the treatment of immune-mediated inflammatory conditions such as PsA, psoriasis, rheumatoid arthritis (RA), Behçet's disease (BD), and ankylosing spondylitis. The current ERA covers the indications psoriasis and PsA.

The partition coefficient (n-octanol/water) for Apremilast was experimentally determined by the shake flask method (comparable to OECD Test Method 107). The resulting log Kow value of Apremilast was 1.77 and hence is below 4.5 (i.e. logKow = 1.77). Therefore, Apremilast cannot be identified as a persistent, bioaccumulative and toxic (PBT) or a very persistent and very bioaccumulative (vPvB) substance. The estimation of the predicted environmental concentration (PEC) has been based on a refined market penetration factor (F_{pen} = 0.0342), and a maximum daily dose of 60 mg. The Phase I $PEC_{SURFACEWATER}$ of Apremilast (1.03 µg/L) exceeds the action limit of 0.01µg/L, triggering a Phase II environmental fate and effects assessment.

Table 15: Summary of main study results

Substance (INN / Invented Name):Apremilast / CC-10004			
CAS-number (if available): 608141-41-9			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log K_{ow}	Shake flask method comparable to OECD107	Log K_{ow} = 1.77			Potential PBT: No
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, F_{pen} = 0.0342	1.03	µg/L			> 0.01 threshold: Yes
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	Not Stated	*Sludge:* *Kd: 28.7-40 L/kg (n=2)* *Koc: 70-91 L/kg (n=2)* *Soil:* *Koc: 263-457 L/kg (n=3)* *Kd:*			K_d < 3,700 L/kg, K_{ow} <10,000 L/kg Terrestrial risk assessment not considered in Tier B
Ready Biodegradability Test	OECD 301	0-2% biodegradable			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ =1.5 days (SL), 0.6 days (SW) $DT_{50, whole\ system}$ =1.9 days (SL), 0.7 days (SW) Apremilast: ≤ 3% AR in sediment at or after 14 days of incubation; one transformation product at max 17% AR in sediment on day 28			Shifting to sediment <10%; sediment adsorption does not occur. M1 >10%, adsorption occurs
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	3500	µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC	6300	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	7200	µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	$1x10^6$	µg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218				Currently being performed

PNEC values were calculated from the relevant aquatic toxicity studies as outlined below:

	NOEC	**AF**	**PNEC**
$PNEC_{surfacewater}$	3500 µg/L Fish, Early Life Stage Toxicity Test/ *Brachydanio rerio*	10	350 µg/L
$PNEC_{microorganisms}$	$1x10^6$ µg/L *Daphnia magna.* Reproduction Test	10	100000 µg/L
$PNEC_{groundwater}$	630 µg/L Activated Sludge, Respiration Inhibition Test	10	630 µg/L

Ground water assessment:

Entry into the groundwater is considered via bank filtration. Exempted for groundwater assessment are substances with an average Koc >10,000 L/kg or which are readily biodegradable and/or have a DT90 <3 days. Since Apremilast has a Koc <10,000 L/kg and is not readily biodegradable nor has an anticipated DT90 <3 days2, entry into the groundwater is considered via bank filtration.

PECGROUNDWATER is calculated as

$PEC_{GROUNDWATER}$ = 0.25 x $PEC_{SURFACEWATER}$

Hence, $PEC_{GROUNDWATER}$ is 0.257 µg/L

Phase IIa risk evaluation:

Environmental compartment	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC	Trigger value	Conclusion
Surfacewater	1.03	350	0.003	1	No risk
Microorganism	1.03	100000	0.00001	0.1	No risk
Groundwater	0.257	630	0.0004	1	No risk

Phase IIa conclusions:

Based on the PEC/PNEC values are below the respective trigger it can be concluded that Apremilast is unlikely to represent a risk to the aquatic environment, groundwater compartment, or micro-organisms in the STP. Since metabolites of Apremilast are expected to be less toxic than parent based on reduced pharmacological activity, and as $PEC_{SURFACEWATER}$ values are expected to be lower than those calculated in Phase I for parent Apremilast (as transformation is not expected to result in one single metabolite), it is concluded that also the metabolites of Apremilast will not represent a risk to the the aquatic environment, groundwater compartment, or the STP.

The log K_{ow} of Apremilast is < 3 and there are no other alerts for bioaccumulation (i.e. Apremilast is not highly adsorptive). Therefore, a bioconcentration study is not indicated and the risk for bioaccumulation is considered acceptable. Since the K_{oc} is <10,000 L/kg, Apremilast is not expected to bind to sewage sludge in the STP, and the exposure of the terrestrial compartment as a result of application of sludge to soil is considered low. Further testing in the terrestrial compartment is not necessary.

Apremilast is not readily biodegradable. The results of the water/sediment study demonstrate significant shifting of a transformation product of Apremilast to the sediment layer, with levels of total radioactivity exceeding 10% of applied at and after day 14 (i.e. max 17% of AR on day 28). These results trigger the consideration of risk to sediment-dwelling organisms in Phase II Tier B; a chronic sediment toxicity study (Chironomid test; OECD 218) is therefore currently being performed.

The CHMP recommends that the applicant submits the GLP-compliant study of appropriate design to determine the partition coefficient of apremilast, and an updated Environmental Risk Assessment (ERA) inclusive of the updated value.

2.3.6. Discussion on non-clinical aspects

The pharmacology of apremilast was comprehensively characterised in studies comprising PDE4 binding

assays, investigations of effects on inflammatory pathways in *in vitro* cellular models to determine a mechanism of action, and studies of anti-inflammatory activity in various animal models of disease. *In vitro* enzyme assays identify apremilast as a potent and selective inhibitor of PDE4, with highly selective inhibition over other PDE enzyme subtypes (279- to 40,000-fold). Analysis of the apremilast human metabolites indicated that only metabolites M7 and M17 have comparable PDE4 inhibitory activity to the parent, account for less than 1% of the apremilast plasma exposure and are therefore not anticipated to contribute to the clinical pharmacodynamic effects. In further affinity screens of binding to 68 cell surface receptors and for inhibition of 17 enzymes, and a kinase inhibition screen of 255 kinases apremilast was not found to cause inhibition at clinically relevant concentrations.

A large body of *in vitro* studies were undertaken to determine the cellular mechanism of action of apremilast. As the proposed anti-inflammatory mechanism involves increased intracellular cAMP levels leading to modulation of CREB/ATF-1 transcription factors and downstream inflammatory mediators, assay endpoints focused on effects on gene and protein expression of these pre- and anti-inflammatory mediators. Generally in stimulated whole blood cells, PBMCs and primary T-cells, apremilast inhibited TNF-α and IL-12 production and increased IL-10 production. IL-6 production was conversely potentiated by apremilast in LPS-stimulated HPBMCs, although in LPS-stimulated whole blood, IL-6 increases were potentiated only in rodent whole blood and not human or monkey whole blood. The CHMP acknowledged that IL-6 potentiation was seen in LPS-stimulated human PBMCS in study 5424-11 and not study 5042-107. The EC_{50} for IL-6 induction with ampremilast was 11 µM in this study with a maximum IL-6 induction of ~2 fold at 100 µM. The applicant stated that the steady state C_{max} is 1.45 µM, so the non-clinical finding is of limited clinical relevance as the effective concentration is supratherapeutic. Furthermore, IL-6 levels were assessed in the phase 3 Clinical Study CC-10004-PSA-002. Compared to baseline IL-6, apremilast was associated with a decrease in IL-6 levels which was statisticallt significant. The CHMP agreed that the decrease in IL-6 is purported to be secondary to TNF-α reduction.

The data provided supported the mechanism of action whereby PDE4 inhibition modulates downstream inflammatory cascades, thus inhibiting the inflammatory response. *In vitro* findings were supported by *in* vivo disease models of inflammation, as apremilast inhibited TNF-α production in response to LPS and carrageen stimulation in rats. The *in vivo* models of arthritis and psoriasis provided evidence to support the proposed clinical indications. Apremilast appeared to decrease arthritis parameters in rats and mice at around 5-25 mg/kg/day, although this did not consistently correlate with histological findings, possibly because the disease induction was not severe. In human skin xenograft mouse models of psoriasis, apremilast demonstrated reduction in disease and expression of the inflammatory markers TNF-α, HLA-DR and ICAM-1.

Cereblon binding studies were undertaken due to structural similarities between apremilast and thalidomide. The lack of competitive binding indicated that apremilast did not bind endogenous cereblon. The CHMP considered this is in agreement with the chemical structure of apremilast, which contains a dialkoxyphenyl moiety instead of the amino-glutarimide ring which facilitates cereblon-binding in thalidomide, lenalidominde and pomalidomide.

The applicant performed a core battery of safety pharmacology studies, with an integrated respiratory and cardiovascular study. In the Irwin's test, lacrimation, ptosis and apathy were seen ≥1000 mg/kg, and one animal died following a 2000 mg/kg dose. The NOEL of 500 mg/kg provides a 12.9-fold or 15.4-fold safety margin based on C_{max} or AUC_{24h}, respectively, from the proposed clinical dose. The study did not indicate a CNS safety concern at clinically relevant doses. Respiratory/cardiovascular safety was investigated following intravenous injection of apremilast. The route of administration of apremilast in the respiratory and cardiovascular safety study in dogs was justified by the applicant based on the limitations of oral administration to anaesthetized dogs, which is acceptable to the CHMP. Respiratory effects in dogs

were limited to moderately increased peak inspiratory and expiratory flow. Apremilast caused a dose-dependent increase in heart rate and left ventricular maximum rate of change, and decreased RR and QT intervals. QTc was unchanged. The IC_{50} for the inhibitory effect of apremilast on hERG current in HEK cells was estimated to be 184.2 µM (84.8 µg/mL) which represents a margin of 127-fold over the expected clinical Cmax and does not indicate a potential risk of QTc prolongation. Furthermore a clinical QT/QTc study did not indicate any treatment related effects up to 50 mg BID. Gastrointestinal motility, which may be decreased by PDE4 inhibitors, was unaffected by apremilast at up 1000 mg/kg. There is no safety margin from NOEL of 0.5 mg/kg and the expected clinical exposure; thus a potential for a possible for effect of aprelimast on the heart rate cannot be excluded (and will be further investigated as desrcribed in the RMP).

In vitro studies indicated that apremilast may act synergistically with PGE2 to decrease TNF-α mediated lung fibroblast recruitment, and expression of pro-angiogenic factors. Some synergistic inhibition of psoriasis-related cytokines was demonstrated with cyclosporine or ETAN in stimulated human T cells and HPBMCs. In vivo studies demonstrated that apremilast had a synergistic anti-arthritic effect with ETAN and methotrexate in mouse arthritis models. In a mouse xenograft model of psoriasis, apremilast showed some synergistic efficacy with methotrexate, although less than higher dose of methotrexate alone.

Following oral doses absorption, apparent clearance was higher in male than female rats, indicating significant first pass metabolism. The gender-difference in bioavailability in rats is reflected in the significantly greater sensitivity of female rats to apremilast in toxicity studies. During the procedure the applicant has clarified with supporting literature references that sex-related differences in exposure are common in rats. The increased exposure in rats is consistent with greater oxidative metabolism in male rats compared to female rats. The sex-related differences were not seen in non-human primates or in humans. Therefore the large differences in exposure between male and female rats are not clinically relevant.This was agreed by the CHMP. In female rabbits, clearance was rapid and bioavailability was negligible (<0.1%) following oral administration, which suggests that the rabbit is not a suitable species for toxicity studies. With the exception of mice, oral doses had relatively short apremilast half lives, and radioactivity half lives were substantially higher, suggesting significant exposure to metabolites of apremilast.

The tissue distribution of [14C]-apremilast-derived radioactivity was determined in albino and pigmented mice by quantitative whole body autoradiography. Rapid distribution was evident with radioactivity in all tissues measured by 2 hours. Highest levels were present in kidney and liver, in line with excretory routes. Radioactivity was relatively highly distributed to pancreas and gastrointestinal mucosa. Distribution to the CNS, indicating blood barrier permeability, and reproductive organs was evident at 24 hours but not detectable by 72 hours post dose. Radioactivity was not detected in any tissues at 168 h after dosing or later. In pigmented mice, levels of radioactivity were elevated in the uveal tracts of the eyes compared to albino mice at 1 and 3 days post-dose. In pregnant mice, apremilast was measurable in fetal plasma at concentrations lower or equal to maternal plasma levels, indicating apremilast crosses the placenta and results in significant fetal exposure. In lactating mice, apremilast was detected in milk at greater levels than plasma (~1.5 fold), indicating lacteal excretion and potential for lacteal transfer to offspring. In vitro plasma protein binding studies found apremilast was 88.6%, 90.6%, 80.9% 84.% and 68% bound in mouse rat rabbit monkey and human plasma, respectively. The data indicate that all species used for toxicity studies have similar levels of plasma protein binding, but all are substantially lower than in human.

Studies in liver microsomes indicated that apremilast is subject to multiple metabolic pathways, namely non-enzymatic (hydrolysis of phthalimide ring leading to M1 and M2), non-CYP-dependent hydrolysis (*N*-deacetylation leading to M7) and CYP-dependent oxidation (*O*-dealkylation to M3 and other minor

metabolites). No sex differences in metabolism were observed in any species, except rat. Human hepatocyte studies were compromised by significant metabolism in negative controls with increased M1/M2 and M18. Metabolism was much higher in rabbits than other species (up to 30% compared to 0.8-26%). All the metabolites formed by human liver microsomes and hepatocytes were formed by one or more animal species. There were no significant differences between in vitro metabolic profiles in adult and juvenile hepatocytes in humans, or microsomes in humans or mice, indicating the species are suitable for juvenile toxicity studies.

In vivo metabolites were quantified in mouse, rat and monkey plasma and excreta. In mice apremilast was extensively metabolised by hydrolysis, oxidative metabolism and subsequent glucuronidation. Following oral dosing parent drug was the highest analyte in males but not in females. Hydrolysis products M1 and M2 were the major circulating plasma metabolites and M15 to a lesser degree. M3, M9, M19 and M22 were also present. In rats, significant differences were seen in the plasma metabolite profile in males and females. In males little or no apremilast was seen, and M12 accounted for 43% of dose, whereas apremilast was the principle component in females, followed by M1 and M2. The increased circulating parent drug in females corresponds to the greatly increased sensitivity seen in toxicity studies in females. Excreta profiles were qualitatively similar between sexes with about 25% of dose recovered as M3, and M9 and M12 also present at 4-7%. In rabbits, no parent drug was measurable in plasma was measurable and metabolites were not determined. In monkeys, metabolism was extensive by 24 post dose, with M1, M2 and M12 and two polar metabolites MkP2 and MkP3 present at the greatest levels. Metabolism was extensive with less than 1% of parent drug identified in excreta. The predominant faecal metabolite was M3, while the primary urinary metabolite was M12. Overall apremilast underwent extensive metabolism in mouse rat and monkey. Each of the major metabolites was present in at least one animal used for toxicity studies. M12 was present in human plasma at higher proportion than all species with the exception of male rats. However M3 and M12 exposures were measured at greater than the expected human exposure as part of the 6 month mouse toxicity study and 12 month monkey toxicity study. The metabolites are therefore considered toxicologically qualified. The applicant will test M12 in *in vitro* induction studies on CYP2B6 and CYP1A2 (as as described in the RMP).

In mice and monkeys apremilast was primarily excreted through feces, with approximately 71% and 73% recovered by 48 hours in male and female mice respectively, and around 68% in monkeys. Urinary excretion was responsible for <5%. There was no indication of sex-related differences in elimination rates in mice or monkey. The data indicated that excretion was extensive, with total recovery at 48 hours over 90% in mice, and near-complete recovery in monkeys at 168 hours. In bile duct cannulated mice, the majority of dose was eliminated in bile, indicating that biliary excretion is the major route of elimination in mice. In rats, elimination was incomplete, most likely owing to the 24 hour duration of the study. However the amount recovered was similar to that in mice at 24 hours, which indicated excretion would likely be extensive at later time points. The fecal route also appears to be the major route of excretion in rats. Initial recovery of radiation was greater in males, indicating slower excretion rates in females, in agreement with overall exposure levels seen in female rats. Comparison across animal species was consistent, with fecal excretion the primary route in each species, and urinary excretion a minor route. However in humans, urinary excretion is the primary route of elimination with 57% of dose recovered in urine and less than 40% in feces. During the procedure, the applicant suggested that the differences in excretion profiles across species do not have any implications for the species used for toxicity studies, as the metabolic pathways and circulating metabolites were comparable and provide safety coverage in the species used for toxicity studies and in humans. This was agreed by the CHMP.

Analysis of apremilast metabolism in human liver microsomes indicated the metabolites M3 and M5 were the major CYP450-dependent metabolites. Subsequent inhibition studies indicate that CYP3A4 is the principle enzyme responsible for metabolism to both M3 and M5, although CYP1A2 and CYP2A6 may also

contribute to the conversion. The CHMP concluded t that some inhibition of CYP2C8 was seen with apremilast, with a roughly 38 fold safety margin, so this inhibition in not clinically relevant.

In an in vitro CYP450 induction assay, apremilast caused a small decrease in activity of CYP1A2 and CYP2C9 although this was not apparent in the inhibition assay. CYP3A4 induction was apparent at with a 3.7-fold induction 100 µM. This concentration is roughly 70 times the expected clinical C_{max} and therefore is not considered clinically relevant.

In P-glycoprotein assays in LLC-PK1 cell lines, apremilast was demonstrated to be actively transported by P-glycoprotein, as ketoconozole inhibited transport by 92%. Apremilast was itself a weak inhibitor of P-glycoprotein, with an $IC_{50} \geq 50$ µM. The finding is described in the product information. Interaction studies with a range of transporters did not find significant inhibition of P-glycoprotein, BCRP, MRP1, MRP2, MRP4, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3, and neither appeared to be a substrate for BCRP, OAT1, OAT3, OATP1B1, OATP1B3 or OCT2.

Acute oral minimum lethal dose was >2000 mg/kg in mice and 2000 and 300 mg/kg in male and female rats, respectively. The data did not indicate a potential for acute systemic toxicity in humans at the expected clinical dose.

The mouse was chosen as the rodent species for repeat dose studies based on metabolism and pharmacokinetic data. Specifically metabolites M3 and M7 were not seen in rat liver microsomes, but seen in human microsomes, and large gender differences in exposure were seen in rats. Overall the choice of rodent species is acceptable to the CHMP. In mice, daily oral administration for up to 6 months was generally associated with increased body weight gain and food consumption. The most significant pathology findings in mice were vascular and perivascular inflammation seen in the heart, thoracic organs, kidney and lung, thymus, mesentery, pancreas and liver, which was accompanied by inflammatory lesions and degenerative vascular changes. These findings correlate with neutrophilia, lymphocytopenia, and changes in clinical chemistry characterised by decreased plasma albumin and increased globulin. The chronic mouse study NOAEL of 10 mg/kg/day corresponds to a lower AUC_{24} value than is expected clinically; therefore no safety margin exists based on plasma exposure.

In cynomolgus monkeys treated for up to 12 months, adverse findings included mortality, decreased body weight, emesis and/or reflux, and some changes in haematology and clinical chemistry parameters. Isolated occurrences of vascular inflammation were seen in the one month study. Myocardial inflammation was also seen in monkeys given 1000 mg/kg/day apremilast for 2 weeks (12.8-fold clinical safety margin from NOAEL). These findings were not seen in the 12 month study, however some small foci of chronic inflammation were seen in the heart at all doses. The applicant considered that the small foci of chronic inflammation in the heart were not treatment-related, as the findings occurred in control and treatment groups. In support of this, a report by Chamanza ¬et al was referenced. The report found that in 570 control cynomolgous macaques, the average incidence of inflammatory cell foci was 25.8%, and in some cases 100% of control animals were affected. Focal myocarditis and myocardial degeneration/fibrosis was seen 6.3% and 5.6% of animals respectively. Due to the low number of animals used per group in the monkey repeat-dose studies, extrapolation is not possible, but generally the data is consistent with the findings seen in the monkey studies with apremilast. In the 14 day dose range-finding study, the applicant stated that treatment-related moderate multifocal myocardial inflammation and haemorrhage and myocardial degeneration were observed in two of three animals at 1000 mg/kg/day. These findings were also seen in one animal at 200 mg/kg/day. However the absence of findings at the 500 mg/kg/day dose, suggest that the findings were not dose-dependent. Moreover the findings were not seen in studies with longer duration, which supports the conclusion that the findings could be attributable to hypersensitivity myocarditis. Overall the conclusions on the findings in the heart of monkeys administered apremilast are acceptable to the CHMP.

This pro-inflammatory effect in the vasculature is considered by the applicant to be specific to rodents, as vasculitis was not seen in the cynomolgus monkey studies or in clinical studies to date. In an in vitro study, LPS-induced IL-6 production was potentiated by PDE inhibitors including apremilast and roflimulast in rodent blood but not human or monkey blood (Report 5265-117). However in another study performed by the applicant (Report 5424-11) apremilast also potentiated the LPS-induced elevation of IL-6 in human PBMCs, indicating pro-inflammatory potential in humans. Therefore the data do not robustly support the proposed mechanism. The applicant provided supportive evidence of species-specificity based on literature reports. The literature does indicate a class-related pro-inflammatory effect of PDE4 inhibitors in rodents, and previous studies are consistent with the histopathological findings the vasculature with accompanying pro-inflammatory haematology and clinical chemistry markers (Larson et al 1996; Dietsch et al 2006; Zhang et al 2008). Moreover the sensitivity of rodents may be explained by a greater contribution of PDE4 to overall PDE cardiac activity in rodents (50%) versus human (10%) hearts. Although the mechanism of toxicity in rodents is not elucidated, and therefore the human relevance is uncertain, the findings are consistent with other PDE4 inhibitors, and in the absence of clinical evidence of vasculitis or changes in clinical lab tests or markers of inflammation, the nonclinical findings do not appear to present a clinical safety concern. These findings have been described in the product information. This was agreed by the CHMP.

Toxicokinetic data confirmed that the nonclinical species were exposed at or above expected therapeutic levels based on AUC values for patients receiving 30 mg BID. The NOAEL AUC levels from the pivotal 6 month repeat dose mouse studies provided no safety margin from the expected clinical dose. The NOAEL AUC levels in primates provide a 5.8- and 3.7-fold safety margin from the expected clinical dose. Reproductive toxicity NOAELs provided little or no safety margin from the expected clinical dose. The metabolites M3 and M12 were identified in the chronic mouse/monkey and monkey studies, respectively at NOAEL levels substantially greater than those seen in humans. The CHMP considered that the metabolites are qualified for general toxicity by the repeat dose studies.

The applicant has performed the standard battery of genotoxicity studies, in line with ICHS2A/B; the studies did not indicate any genotoxic potential. 2 year carcinogenicity studies were performed in mice and rats, in line with ICH S1. In mice, neoplastic findings of malignant lymphoma in males and skin sarcoma in males and females were not considered to be attributable to apremilast. Incidence of sarcomas were attributed to microchip tagging, which is well characterised in the literature. Incidence of malignant lymphoma in males appeared to decrease with increasing dose. This is most likely due to the atypically high number of findings in the control group (20% compared to historical incidence of 7.6%). However, as there was no dose-dependent increase in tumours, and all groups were within the expected incidence for this type of finding (4.5-8.6%), the atypical control findings are not considered to have masked any apremilast-related effects. In rats, there was no evidence of carcinogencity. Taken together, the CHMP concluded that the rodent bioassays indicate that apremilast is not carcinogenic.

The selection of mouse and monkey for reproductive and developmental toxicity is justified by the unfavourable metabolite profile and sex-related exposure differences in rats, and the lack of measurable exposure to apremilast in rabbits, respectively. The justification is acceptable to the CHMP. In the initial fertility study, fertility indices and matings were decreased, and time to mating was increased. No NOAEL was established and post-implantation losses were also increased at all apremilast doses, and the average number of viable embryos was reduced at 1000 mg/kg. In the subsequent female fertility and EED study, apremilast was associated with reduced number of estrous cycles, longer estrous cycle length, and longer time to mate. However fertility indices were not affected. Apremilast decreased fertility in mice when both males and females were dosed. Changes in male reproductive organ weight were not correlated with histopathological findings. In apremilast-treated females the number of estrous cycles was reduced and cycle length prolonged, without decreased fertility indices when mated with untreated

males. The NOAEL for functional effects on fertility provide a 2.9-fold and 4.0-fold safety margin from the clinical dose in males and female.

Consistent finding in all the studies with dosing during gestation was toxicity to the offspring, including lethality, both in utero and post-natally. In the embryo-fetal development studies, the maternal and developmental NOEL in mice and monkeys were 10 and 20 mg/kg/day (1.3- and 1.4-fold clinical AUC), respectively. In a pre- and postnatal study, the NOEL for maternal toxicity and F1 generation was 10 mg/kg/day (1.3-fold clinical AUC). There was evidence of dystocia at 300 mg/kg/day and to a lesser extent at 80 mg/kg/day.

Although NOAELs were identified for the reproductive toxicity studies, there is no safety margin for the effects on survival of the conceptuses.

Apremilast was shown to cross the placenta in monkeys and was excreted in the milk of mice.

The absence of defining the dose-response in the mouse to establish whether malformations are induced at a dose intermediate between the NOAEL and a dose inducing lethality, and the absence of information on the abortuses in the monkey study are the main deficiencies. Of note, the pattern of intra-uterine and post-natal deaths seen with apremilast in rodents is frequently seen with cardiovascular teratogens. Given that apremilast has anti-VEGF activity, and has been demonstrated to inhibit sprout formation from human umbilical cord vessels, its potential to cause cardiovascular abnormalities cannot be excluded. Although none have been reported, it is not clear from the mouse study report how thoroughly the heart and major blood vessels were examined for malformations. The applicant clarified that the mice fetuses were examined for cardiovascular malformations in the Combined Fertility and Developmental Toxicity Study using a modified Wilson's sectioning technique (test facility training manual, SOP and historical control data provided). There were no heart or great vessel findings. The applicant confirmed that aborted fetuses were not evaluated for malformations, as they were not adequately developed to facilitate examination of developmental defects. The applicant also clarified that the possibility that malformations can occur in the embryos that are lost prior to scheduled cesarean section cannot be ruled out. In the mouse, these early prenatal losses typically manifest as implants undergoing resorption at the time of cesarean section; therefore, no fetal morphological examination can be performed. In the monkey, pregnancy losses usually occur as abortions, and the aborted fetal tissues are usually degenerated and cannot be evaluated morphologically. The CHMP acknowldeged the inability to identify potential malformations in embryos lost prior to caesarean section, due to degeneration of the fetal tissues in monkeys, and resorptions of implants in mice. The product information was amended to mention that the effects 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. During the procedure the CHMP requested the SWP's opinion as to whether a contra-indication for pregnancy is justifiable for apremilast on the basis of animal data only. The SWP considered that following administration of apremilast, pre-natal deaths occurred in all combined or standalone embryo-foetal development toxicity studies in both species tested (mice and monkeys) and that minimal clinical data are available. As of 15 May 2013, 21 pregnancies (7 female subjects and 14 partners of male subjects) were reported during the apremilast clinical trials. There were no congenital anomalies reported for any subject or partner of male subjects who became pregnant while being exposed to apremilast therapy. However it could be argued that miscarriage/post-implantation loss could occur before the patient knew they pregnant and as such, these data would not be captured. The following considerations have been made with respect to the fact that only animal data would be the basis for a contra-indication: Small safety margins (1.3 and 1.4 for mice and monkeys respectively) in reproductive and developmental toxicity studies; Apremilast has anti-angiogenic properties and thus potential induction of malformations cannot be excluded. Early embryolethality may have masked these malformation effects; Psoriatic arthritis and

chronic plaque psoriasis are not life-threatening conditions and that other treatments are available or that treatment could be modified/deferred/avoided.These considerations are in line with sections 8.2.1.2 and 8.2.1.3 of the Guideline on Risk assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (EMEA/CHMP/203927/2005). The SWP therefore considered that apremilast should be contra-indicated during pregnancy. At the CHMP's request, a contraindication in pregnancy has therefore been included by the applicant in the product information.

Increased weight gain was seen in mice both prior to mating in the combined fertility and embryo-fetal development study and in repeat-dose toxicity studies. While this effect is considered to be treatment-related, the applicant argued that it is not adverse based on lack of histopathological findings or clinical correlation. While gravid uterine weight was not recorded in the combined fertility and EFD study, the applicant has discussed available data from a separate EFD study in which mean maternal body weights (corrected for gravid uterine weight) were similar between control and apremilast-treated groups. The historical control rate for scoliosis in monkeys has been provided by the test facility. According to the Covance memo, 3 incidences of scoliosis have been detected out of 634 control monkey fetuses (>0.005 %). There were only 3 live fetuses for evaluation in the 1000 mg/kg/day group, one of which was affected with scoliosis which equates to an incidence of 33.3 % in this group. However, given that scoliosis is widely accepted to have familial origins and that adequate safety margins exist between the exposure at which this finding was seen and that anticipated through clinical use of apremilast, this finding is not considered to be of clinical relevance. The applicant has presented the incidence of rotated hindlimbs in the combined fertility and embryo-fetal development study in mice as both litter incidence and fetal incidence to account for the increased embryo-fetal mortality observed at higher doses. It was agreed by the CHMP that the fetal incidence did not increase in a dose-dependent manner and the values were generally within the incidences observed historically at the testing facility or just slightly outside of the upper end (2.1%) of the historical control range. The applicant's conclusion that this finding was not toxicologically meaningful is accepted by the CHMP.

In a juvenile mouse study, apremilast was associated with increased mortality within the first week of treatment. Over 90 days treatment was generally well tolerated, indicating that animals were initially more susceptible to treatment. The study did not highlight any toxicities specific to juvenile animals. Local tolerance and phototoxicity studies did not indicate potential safety concerns. Metabolites of apremilast are toxicologically qualified based on their presence in mouse and monkey in the general toxicity studies. The potential for immunotoxicity was discussed by the applicant, and was assessed in the context of the repeat dose studies above. Overall the effects on the immune system was generally sufficiently characterised in the existing nonclinical package, notwithstanding concerns in monkeys.

Based on the 8-fold lower PDE4 inhibition of CC-10007, adverse effects of the R-enantiomer due to exaggerated pharmacology are not expected. A comparative toxicity study in female rats demonstrated that CC-10007 did not cause the general toxic effects associated with the apremilast. In order to qualify the impurity RC6 in the in vitro bacterial reverse mutation assay, apremilast was spiked with 5% w/w RC6, which gave a maximum concentration of 250 µg/plate (5000 µg apremilast/plate). However, as precipitate was seen at the highest concentration, the RC6 impurity may not have been tested at 250 µg/plate, which is the detection limit for most relevant mutagens in the Ames test (Kenyon et al., Reg Tox & Pharm, 2007, 75-86; Questions and answers on the 'Guideline on the limits of genotoxic impurities (EMA/CHMP/SWP/431994/2007 Rev. 3)). During the procedure, the applicant clarified that the impurity RC6 was qualified based on its presence in the mouse carcinogenicity study and the in vitro Ames test. Given that RC6 is also the animal metabolite M7, the impurity exposure in the carcinogenicity is expected to be 2-3 fold greater than the level in humans at 30 mg BID. Therefore, in line with ICH M7, the impurity is considered qualified as it was present at a greater concentration than will be achieved from exposure through the drug substance. The applicant's justification is acceptable to the CHMP.

A Phase I and Phase IIa environmental risk assessment was performed. Apremilast is not expected to pose a risk to the environment. The applicant will submit the GLP-compliant study of appropriate design to determine the partition coefficient of apremilast, and an updated Environmental Risk Assessment (ERA) inclusive of the updated value.

2.3.7. Conclusion on the non-clinical aspects

In vitro pharmacological characterisation determined apremilast to be a potent and selective inhibitor of PDE4 highly selective inhibition over other PDE enzyme subtypes and various enzymes and kinases. As the proposed anti-inflammatory mechanism involves increased intracellular cAMP levels leading to modulation of CREB/ATF-1 transcription factors and downstream inflammatory mediators, in vitro activity endpoints focused on effects on gene and protein expression of these pre- and anti-inflammatory mediators. Generally in stimulated whole blood cells, PBMCs and primary T-cells, apremilast inhibited TNF-α and IL-12 production and increased IL-10 production. *In vitro* findings are supported by efficacy in in vivo disease models of inflammation including rodent models of arthritis and psoriasis.

Safety pharmacology studies did not indicate a CNS or respiratory safety concern, or effects on gastrointestinal motility, at clinically relevant doses. In dogs apremilast was associated with dose-dependent increase in heart rate and left ventricular maximum rate of change, and decreased RR and QT intervals, although QTc was unchanged. In vitro hERG inhibition assays revealed no clinically relevant risk of QTc prolongation.

The pharmacokinetics of apremilast has generally been well characterised by the applicant.

Based on the small safety margins (1.3 and 1.4 for mice and monkeys respectively) in reproductive and developmental toxicity studies and that psoriatic arthritis and chronic plaque psoriasis are not life-threatening conditions and that other treatments are available or that treatment could be modified/deferred/avoided, the CHMP considered that apremilast should be contra-indicated during pregnancy in line with sections 8.2.1.2 and 8.2.1.3 of the Guideline on Risk assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (EMEA/CHMP/203927/2005). This was agreed by the applicant and the product information has been updated accordingly.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The Apremilast clinical development program for the treatment of psoriatic arthritis comprises one Phase 2 study (Study PSA 001) and four Phase 3 studies: PSA-002, PSA-003, PSA 004, and PSA-005.

The three replicate pivotal Phase 3 studies (PSA-002, PSA 003, and PSA-004) are conducted in subjects with inadequate response or intolerance to small-molecule DMARDs and/or biologic DMARDs. The

supportive study PSA-005 evaluated apremilast as a monotherapy. All 4 studies are in the long-term extension phase. The 52-week data from the three pivotal Phase 3 studies (PSA-002, PSA 003, and PSA-004) and 24-week data from the fourth Phase 3 study (PSA-005) are included in this submission.

Studies PSA 002, PSA 003, and PSA 004 are considered to be pivotal studies.

Phase 2 study

Study Number	No. of Centres (1)	No. of Subjects: Randomized / Completed (2) / Dropouts	Population / Design / Control	Route and regimen	Subject Demographics: Sex Mean Age Race	Primary Endpoint
PSA-001	38	204 randomized 165 completed Treatment Phase 39 withdrew prior to end of Treatment Phase	Population: Subjects with active PsA; concomitant MTX allowed. Treatment groups stratified by baseline MTX use. Treatment Phase: R, D-B, P-C, P-G study. Duration: 84 days Following completion of Treatment Phase, placebo subjects re-randomized to APR 20 BID or APR 40 QD. Extension Phase: R, DB active treatment, PG study. Duration: 84 days	Oral dosing APR 40 QD: 10 mg QD on Days 1-3, 20 mg QD on Days 4-7, 40 QD on Days 8-85. APR 20 BID: 10 mg QD on Days 1-3, 20 mg QD on Days 4-7, 20 mg BID on Days 8-85.	107 male, 97 female 50.6 years (range, 21 – 81 years) 197 white, 3 Asian/Pacific Islander, 1 black, 1 Hispanic, 2 other	Modified ACR 20(3) at Day 85

Three Pivotal Phase 3 studies

Study Number	No. of Centres (1)	No. of Subjects: Randomized / Completed (2) / Dropouts	Population / Design / Control	Route and Regimen	Subject Demographics: Sex Mean Age Race	Primary Endpoint
PSA-002 02 Jun 2010 – LTE Ongoing (Last subject's Week 52 visit: 02 Oct 2012)	83	504 randomized 470 completed Wk 16 visit 444 completed Wk 24 visit 373 completed Wk 52 visit 131 withdrew prior to Wk 52	Population: Subjects with active PsA and inadequate response to ≥ 1 small-molecule or biologic DMARD; concomitant small-molecule DMARDs allowed. Treatment groups stratified for baseline DMARD use. Placebo-Controlled Phase: : R, D-B, P-C, P-G study.	Oral dosing APR 20 BID: Titration by 10 mg per day in divided doses: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4 and thereafter.	249 male, 255 female 50.4 years (range, 19 – 83 years) 455 white, 24 Asian, 3 Native Hawaiian/ Pacific Islander, 3 American Indian/ Alaska Native, 2 black, 17 other	Modified ACR 20[d] at Week 16

			Duration: 24 weeks Following completion of Placebo-Controlled Phase, placebo subjects re-randomized to APR 20 BID or APR 30 BID. Extension Phase: R, DB, PG study. Duration: 236 weeks	APR 30 BID: Titration by 10 mg per day in divided doses: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4, 50 mg on Day 5, 60 mg on Day 6 and thereafter, in divided doses.		
PSA-003 27 Sep. 2010 – LTE Engoan (Last subject's Week 52 visit: 27 DEC 2012	84	488 randomized (4 not treated [e] 448 completed Wk 16 visit 428 completed Wk 24 visit 361 completed Wk 52 visit 127 withdrew prior to Wk 52	Population: Subjects with active PsA and inadequate response to ≥ 1 small-molecule or biologic DMARD; concomitant small-molecule DMARDs allowed. Treatment groups stratified for baseline DMARD use. Placebo-Controlled Phase: R, D-B, P-C, P-G study. Duration: 24 weeks Following completion of Placebo-Controlled Phase, placebo subjects re-randomized to APR 20 BID or APR 30 BID. Extension Phase: R, DB, PG study. Duration: 236 weeks	Oral dosing APR 20 BID: Titration by 10 mg per day in divided doses: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4 and thereafter. APR 30 BID: Titration by 10 mg per day in divided doses: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4, 50 mg on Day 5, 60 mg on Day 6 and thereafter, in divided doses.	209 male, 275 female 50.9 years (range, 19 – 80 years) 460 white 13 Asian 4 black 6 other 1 missing	Modified ACR 20[d] at Week 16

PSA-004 30 Sep 2010– LTE Ongoing (Last subject's Week 52 visit: 28 Jan 2013	78	505 randomized 469 completed Week 16 visit 438 completed Week 24 visit 368 completed Week 52 137 withdrew prior to Week 52	Population: Subjects with active PsA and inadequate response to ≥ 1 small-molecule or biologic DMARD; ≥ 1 qualifying psoriasis lesion ≥ 2 cm; concomitant small-molecule DMARDs allowed. Treatment groups stratified for baseline DMARD use and extent of psoriasis (BSA). Placebo-Controlled Phase: R, D-B, P-C, P-G study. Duration: 24 weeks Following completion of Placebo-Controlled Phase, placebo subjects re-randomized to APR 20 BID or APR 30 BID. Extension Phase: : R, DB, PG study. Duration: 236 weeks	Oral dosing APR 20 BID: Titration by 10 mg per day in divided doses: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4 and thereafter. APR 30 BID: Titration by 10 mg per day in divided doses: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4, 50 mg on Day 5, 60 mg on Day 6 and thereafter, in divided doses.	236 male, 269 female 49.7 years (range, 18 – 77 years) 482 white 15 Asian 2 black 1 Native Hawaiian/ Pacific Islander 5 other	Modified ACR 20[d] at Week 16
PSA-005 09 Dec 2010 – LTE Ongoing (Last subject's Week 24 visit: 14 Jan 2013)	99	528 randomized (1 not treated)[(f)] 500 completed Week 16 visit 471 completed Week 24 visit 57 withdrew prior to Week 24	Population: Subjects with active PsA previously untreated with DMARDs. R, D-B, P-C, P-G study. Duration: 24 weeks Following completion of Placebo-Controlled Phase, placebo subjects re-randomized to APR 20 BID or APR 30 BID. Extension Phase: : R, DB, PG study. Duration: 236 weeks	Oral dosing APR 20 BID: Titration by 10 mg per day in divided doses: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3, 40 mg on Day 4 and thereafter. APR 30 BID: Titration by 10 mg per day in divided doses: 10 mg on Day 1, 20 mg on Day 2,	250 male, 277 female 49.4 years (range, 18 – 77 years) 520 white 3 Asian 1 American Indian/ Alaska Native 3 other	Modified ACR 20[d] at Week 16

				30 mg on Day 3, 40 mg on Day 4, 50 mg on Day 5, 60 mg on Day 6 and thereafter, in divided doses.		

ACR 20 = American College of Rheumatology 20% response; APR = apremilast; BID = twice daily; BSA = body surface area; DMARD = disease-modifying antirheumatic drug; LTE = active-treatment/long-term safety phase; MTX = methotrexate; PsA = psoriatic arthritis; QD = daily. R=Randomised; D-B= Double blind; P-C= placebo controlled; P-G =parallel group

[a] Number of centers with subjects enrolled.

[b] Start date = first randomized subject's screening date. Completion date (unless ongoing) = last subject's last visit date (on-site visit or follow-up phone call).

[c] Completed all treatment phases of the study (i.e., early withdrawal during follow-up period is not considered non-completion).

[d] Modified ACR 20, defined as ≥ 20% improvement in 78- and 76-joint count of tender and swollen joints, respectively, and a ≥ 20% improvement in 3 of the following 5 assessments: patient's (subject's) global assessment of disease activity (PGA), evaluator's (physician's) global assessment of disease activity (EGA), subject's assessment of pain, Health Assessment Questionnaire Disability Index (HAQ-DI), or C-reactive protein (CRP).

[e] Four subjects were randomized in error, were not dispensed investigational product, and are excluded from the Full Analysis Set for Study PSA-003.[f] One subject was randomized in error, was not dispensed investigational product, and is excluded from the Full Analysis Set for Study PSA-005.

2.4.2. Pharmacokinetics

The PK of apremilast was investigated in 16 clinical pharmacology studies, and eight phase 2 or 3 studies including subjects with PsA, PSOR or RA.

Based on the intensive and sparse data from these studies, the disposition characteristics of apremilast, in terms of absorption, distribution, metabolism and elimination (ADME), have been derived. Intrinsic factors of hepatic or renal impairment, age, sex, ethnicity, and disease type and their potential impact on PK have also been investigated as well as extrinsic factors including concomitant use with CYP3A4 inhibitors/inducers, methotrexate (MTX) and the oral contraceptive (OC). Finally, an investigation of the potential of apremilast to prolong QT interval completes the package.

The concentration of CC-10004 (Apremilast) and its metabolites, CC-16793 [M14], CC-16557 [M16] and CC-16166 [M12]) in acidified lithium heparin human plasma was determined using LC-MS/MS. Sample preparation involved liquid/liquid extraction prior to analysis.

Absorption

Apremilast is a low solubility compound with a measured solubility of 10.8 – 14.5 µg/ml over the pH range 1 to 8. Data from a mass balance study PK-002 (and an absolute bioavailability/regional absorption study CP-012) have indicated that apremilast is rapidly and well absorbed following oral administration, with a tmax of 1- 3 hours and absolute bioavailability of around 73%. CP-012 has also shown that while oral absorption of apremilast occurs at all regions of GI tract, as might be expected, the major site of absorption (93 %) is the proximal small bowel. Food does not affect oral absorption (CP-022) and kinetics are linear with the area under the curve (AUC) increasing in a dose-proportional manner up to 50 mg BID (or 80 mg QD), which therefore encompasses the proposed therapeutic dose.

Bioavailability

Data from Study CC-10004-PK-002 and Study CC-10004-PK-012 showed that in healthy subjects, apremilast is rapidly absorbed following oral administration along the entire gastrointestinal tract, with an average absolute bioavailability of approximately 73%. T_{max} was between 1 and 3 hours.

The mean total urinary and faecal radioactive recovery of CC-10004 (and its metabolites) was 97.1%, with mean contributions of 57.9% and 39.2% from urine and faeces, respectively.

Study CC-10004-CP-022 demonstrated that oral absorption of apremilast occurs at all regions of the GI tract. By delivering apremilast as a particulate formulation to the proximal small bowel, distal small bowel and colon, the relative bioavailability for each of these regions of the GIT were 90%, 77% and 51% respectively.

Table 10: Summary of Plasma Pharmacokinetic Parameters of Apremilast by Treatment (Pharmacokinetic Population)

Parameter (Unit)	Single 30-mg Apremilast Tablet	
	Fasted (N = 45)	Fed (N = 44)
AUC_{∞} (ng·h/mL)[a]	3157.96 (34.6)	3506.19 (33.9)
AUC_t (ng·h/mL)[a]	3083.05 (34.0)	3436.39 (33.0)
C_{max} (ng/mL)[a]	339.86 (26.5)	333.85 (30.0)
t_{max} (h)[b]	2.50 (0.62, 5.02)	3.00 (1.00, 8.00)
$t_{1/2}$ (h)[a]	8.88 (21.2)	7.99 (18.9)
CL/F (mL/h)[a]	9499.80 (34.6)	8556.28 (33.9)
Vz/F (mL)[a]	121735.96 (38.2)	98582.15 (28.0)

Relative Bioequivalence

One study (CC-1004-BA-001) was designed to compare bioavailability of apremilast capsules made with milled API relative to that of apremilast capsules made with micronized API, under both fasting and fed conditions.

In the fasting state AUC and C_{max} for the micronized capsules were significantly higher than for the milled capsules. AUC was 17% less and C_{max} was 22% less in the milled versus the micronized capsules. Also in the fed state C_{max} was significantly higher for the micronized capsules, although AUC was comparable.

Another study (CC-1004-BA-002) was designed to compare the bioavailability of apremilast delivered as an oral 40 mg tablet to that of two 20 mg apremilast capsules under both fed and fasting conditions. The results of this study are listed in the table 16 below.

Table 16: Summary of PK results

Comparison	Parameter	LSMean Test	LSMean Reference	%Ratio (Test/Reference)	90% CI
TE vs. CE N = 15	C_{max} (ng/mL)	433.6	381.8	113.55	96.30 ; 133.88
	$AUC_{(0-t)}$ (h*ng/mL)	4168.2	3700.9	112.63	100.40 ; 126.34
	$AUC_{(0-\infty)}$ (h*ng/mL)	4205.2	3741.8	112.38	100.16 ; 126.09
TB vs. CB* N = 15	C_{max} (ng/mL)	421.7	333.0	126.61	106.96 ; 149.85
	$AUC_{(0-t)}$ (h*ng/mL)	4318.8	4100.4	105.33	93.63 ; 118.49
	$AUC_{(0-\infty)}$ (h*ng/mL)	4346.7	4131.2	105.22	93.51 ; 118.38
CB* vs CE N = 15	C_{max} (ng/mL)	333.0	381.8	87.22	73.73 ; 103.19
	$AUC_{(0-t)}$ (h*ng/mL)	4100.4	3700.9	110.80	98.53 ; 124.59
	$AUC_{(0-\infty)}$ (h*ng/mL)	4131.2	3741.8	110.41	98.16 ; 124.18
TB vs TE N = 15	C_{max} (ng/mL)	421.7	433.6	97.25	82.48 ; 114.67
	$AUC_{(0-t)}$ (h*ng/mL)	4318.8	4168.2	103.61	92.37 ; 116.23
	$AUC_{(0-\infty)}$ (h*ng/mL)	4346.7	4205.1	103.37	92.13 ; 115.97

* Calculated weighted mean for Subject 9, Treatment CB

Influence of food

Study CC-10004-CP-022 examined the effect of food on the absorption of a single 30mg dose of apremilast in healthy subjects and demonstrates that concentration versus time profiles were similar in both fed and fasted conditions. The 90% CIs of the geometric mean ratios for AUC and C_{max} of fed versus fasted were within the range 80-125%. Table 17 below gives a summary of the PK parameters measured, and Table 18 provides some statistical analysis.

Table 17 Summary of Plasma Pharmacokinetic Parameters of Apremilast by Treatment (Pharmacokinetic Population)

Parameter (Unit)	Single 30-mg Apremilast Tablet	
	Fasted (N = 45)	Fed (N = 44)
AUC_{∞} (ng·h/mL)[a]	3157.96 (34.6)	3506.19 (33.9)
AUC_t (ng·h/mL)[a]	3083.05 (34.0)	3436.39 (33.0)
C_{max} (ng/mL)[a]	339.86 (26.5)	333.85 (30.0)
t_{max} (h)[b]	2.50 (0.62, 5.02)	3.00 (1.00, 8.00)
$t_{1/2}$ (h)[a]	8.88 (21.2)	7.99 (18.9)
CL/F (mL/h)[a]	9499.80 (34.6)	8556.28 (33.9)
Vz/F (mL)[a]	121735.96 (38.2)	98582.15 (28.0)

Table 18: Statistical Analysis of Plasma Pharmacokinetic Parameters of Apremilast (PK Population)

Table 18 Statistical Analysis of Plasma Pharmacokinetic Parameters of Apremilast (Pharmacokinetic Population)

Parameter (Unit)	Treatment	N	Geometric LS Means	Ratio (%) of Geometric LS Means (Fed/Fasted)	90% Confidence Interval of the Ratio of Geometric LS Means	Intrasubject Coefficient of Variation (%)
AUC_t (ng·h/mL)	B (Fed)	44	3467.3	112.4	109.3 – 115.6	7.8
	A (Fasted)	45	3084.0	NA	NA	NA
AUC_∞ (ng·h/mL)	B (Fed)	44	3536.4	112.0	108.9 – 115.1	7.7
	A (Fasted)	45	3158.8	NA	NA	NA
C_{max} (ng/mL)	B (Fed)	44	334.7	98.3	90.7 – 106.6	22.9
	A (Fasted)	45	340.4	NA	NA	NA

AUC = area under the concentration-time curve; AUC_t = AUC from time zero to time t, where t is the last measurable time point; AUC_∞ = AUC from time zero extrapolated to infinity; C_{max} = maximum observed plasma concentration.
Treatment A: a single 30-mg apremilast tablet administered under fasted conditions.
Treatment B: a single 30-mg apremilast tablet administered under fed conditions.
One subject (Subject 1001106) was excluded from the pharmacokinetic (PK) analysis because the subject did not have an evaluable PK profile. Subject 1001143 was excluded from the PK analysis for Period 2 (Treatment B) because the subject did not have an evaluable PK profile in Period 2.
Source: Table 7 of report CC-10004-CP-022

Distribution

After IV administration, the mean volume of distribution was 87L (Study CC-10004-CP-012). Apremilast is moderately bound to plasma proteins at 68%.

Elimination

- **Excretion**

Apremilast is mainly eliminated as metabolites formed via both cytochrome P450 mediated oxidative metabolism and non CYP mediated hydrolysis. Less than 3% of the dose excreted in urine and less than 7% of the dose excreted in faeces is unchanged apremilast. Following IV administration apremilast has a mean total clearance of approximately 10L/hour and a terminal half life of approximately 6 to 9 hours.

- **Metabolism**

ADME Study CC-10004-PK-002 characterised the pharmacokinetic profile of a single oral 20 mg suspension dose of apremilast in healthy male subjects, and found that in line with in vitro findings, apremilast was extensively metabolised into multiple metabolites. Up to 23 metabolites were recovered in urine and faeces. The major metabolic route was O- demethylation, with 50% of the dose metabolised this way. Other metabolic paths include O- deethylation, N -deacetylation, hydroxylation, hydrolysis of the imide ring and various combinations of these pathways. CYP3A4, CYP1A2 and CYP2A6 all participate in apremilast metabolism, however it appears that CYP3A4 is the main CYP enzyme involved. Other isozymes such as CYP2A6 and CYP1A2 seem to play a much less prominent role, but may compensate in the event of CYP3A4 inhibition.

- **Inter-conversion**

Study CC- 10004-PK-005 which primarily evaluated the influence of multiple doses of ketoconazole on the pharmacokinetics of apremilast in healthy adult males also examined for the presence of CC-10007, the R- enantiomer. The study concluded that the R- enantiomer was not present in plasma or urine in any quantifiable amount.

- **Pharmacokinetics of metabolites**

The PK parameters for apremilast and its main metabolites are outlined in table 19 below.

All of the main metabolites are pharmacologically inactive.

The two pharmacologically active metabolites M7 and M17 accounted for less than 1% of the apremilast plasma exposure, and are not anticipated to contribute to the pharmacodynamic effect.

Table 19 Mean (SD) of Plasma Pharmacokinetics Parameters for [^{14}C]-apremilast and Metabolites and Total Radioactivity in Six Male Human Subjects Following a Single Oral Dose of 100 microcuries/20 mg [^{14}C]-apremilast

Parameter (Unit)	TRA Mean (SD)	Apremilast Mean (SD)	M11 Mean (SD)	M12 Mean (SD)	M13 Mean (SD)	M14 Mean (SD)	M16 Mean (SD)
C_{max} (ngEq/mL)	527.46 (126.72)	321.3 (134.2)	20.24 (7.623)	110.6 (36.08)	7.534 (6.760)	9.377 (4.293)	27.57 (26.00)
AUC_t (ngEq·h/mL)	5482.61[a] (825.18)	2455.3 (690.36)	138.97 (88.740)	2123.7 (331.36)	133.14 (124.55)	269.43 (145.76)	363.30 (54.413)
t_{max} [b] (h)	1.51 (1.01-3.01)	1.76 (1.01-2.53)	1.01 (0.547-2.53)	2.51 (1.01-2.53)	2.53 (1.01-24.0)	2.52 (1.01-24.0)	5.27 (1.01-8.02)
AUC_∞ (ngEq·h/mL)	6632.2 (653.07)	2635.9 (705.28)	232.39 (150.99)	2446.2 (416.36)	nc	nc	389.06 (90.983)
$t_{1/2}$ (h)	50.4 (8.65)	7.14 (2.65)	10.7 (10.2)	15.8 (3.93)	nc	nc	11.0 (2.36)
AUCUD or M/ AUCTRA (%)[c]	na	44.78	2.53	38.74	2.43	4.91	6.63

AUC = area under the plasma concentration-time curve; AUCTRA = AUC of total radio activity; AUCUD = AUC of unchanged drug; C_{max} = maximum plasma concentration; M = metabolite; na = not applicable; nc = not calculated, due to insufficient data; SD = standard deviation; TRA = total radioactivity.

[a] AUC_{48} for TRA was calculated in this report to be 5482.6 (825.18) ngEq·h/mL

[b] t_{max} values are reported as median (minimum-maximum).

[c] AUC_t (unchanged drug or metabolite)/AUC_{48} (TRA) ×100%

Source: Table 3 of report CC-10004-PK-002-metabolite

Dose proportionality and time dependency

- **Dose proportionality**

Apremilast demonstrated consistent and comparable dose-proportional exposure in healthy subjects across all the clinical pharmacology studies to 50mg BD or 80mg OD.

In one clinical pharmacology study in subjects with RA or PsA (CC-10004-PK-010) and five phase 2 and 3 studies in subjects with PsA, psoriasis, or RA, apremilast exposure was consistent and comparable, although apremilast exposure does appear to be approximately 40% higher in subjects with PsA, psoriasis, or RA versus healthy subjects.

- **Time dependency**

The pharmacokinetics of ascending multiple oral dosing of apremilast was evaluated in 2 healthy volunteer studies (Studies CC-1004-PK-001 and CC-1004-PK-007). Apremilast displayed rapid absorption with maximum plasma concentrations occurring at a median t_{max} of 1 to 3 hours. Following C_{max} the plasma concentrations declined in an apparent biphasic manner. The mean apparent half life was estimated to be 5 to 7 hours. Steady state was achieved within 24 hours of the start of multiple dosing. Doses up to 40 mg daily did not appear to cause accumulation. There was slight accumulation at 40 mg BD and above. Systemic exposure increased in a dose proportional manner across all doses.

Intra- and inter-individual variability

An objective of 5 Phase 2 and 3 trials was to determine sources of variability in PK parameters. Each of these studies suggested that apremilast exhibits moderate inter subject variability. Between subject variability ranges from approximately 33-43% for CL/F (apparent clearance), and 20-43% for Vc/F (apparent central volume of distribution) were observed. Intrasubject variability for AUC for 6 of the clinical pharmacology studies ranged from 7.7% to 18.6%. For the 2 studies presented where only apremilast was administered, the intrasubject variability for AUC was less than 10%.

Pharmacokinetics in target population

Special populations

- **Impaired renal function**

Study CC- 1004-CP- 019 was carried out to examine the pharmacokinetics of apremilast and its major metabolite M12 in subjects with severe renal impairment and normal renal function. This was a two centre, open label, single dose study. Severe renal impairment was taken as those subjects with an eGFR ≤30 mL/min/1.73 m^2, and normal renal function was defined as eGFR ≥90 mL/min/1.73 m^2. There were 8 subjects enrolled with severe renal impairment and these were compared to 8 healthy subjects with normal renal function. Both groups were comparable in terms of age, gender and weight within reasonable limits. All subjects received a single dose of 30 mg apremilast. Blood samples were taken at incremental timepoints from pre dose until 72 hours post dose. These samples were analysed for both apremilast and M12 concentrations. Non compartmental methods were used to calculate the following pharmacokinetic parameters: $AUC_{0-t,}$ AUC_{0-inf}, C_{max}, t_{max}, and $t_{1/2,}$ CL/F, Vz/F.

In severe renal impairment systemic clearance and the volume of distribution for apremilast were decreased by 46.9% and 32.7% respectively, and $t_{1/2}$ was increased by 2.5 hours. The decrease in clearance resulted in an increase in AUC of 88.5% and an increase in C_{max} of 41.6%. T_{max} appeared to be unaffected by renal function, and was 3 hours in both the severe renal impairment group and the normal renal function group.

In terms of the pharmacokinetics of the M12 metabolite, the differences were more pronounced. $T_{1/2}$ was prolonged by 62% (10.5 hours). The decrease in clearance resulted in an increase in AUC of 191.5% and an increase in C_{max} of 42.9%.

Simulations have suggested that 30 mg QD produces apremilast exposure comparable to a 30mg BD dose in those with normal renal function. A single dose of 30 mg apremilast also appeared to be well tolerated in subjects with severe renal impairment, and their demographically matched subjects with normal renal function. Pooled population PK analysis from 86 subjects with mild and moderate renal impairment has been provided, and this did not show a correlation between creatinine clearance and apremilast clearance.

- **Impaired hepatic function**

The effect of hepatic impairment on the pharmacokinetics of apremilast and its major metabolite M12 was evaluated in human subjects with moderate hepatic impairment and severe hepatic impairment, and compared to age-gender matched volunteers with normal hepatic function and of similar weight (Study CC-10004-CP-011). A total of 32 subjects (male and female) were enrolled; of these 8 had severe hepatic

impairment, 8 had mild hepatic impairment and 16 had normal hepatic function. The degree of hepatic impairment was measured according to the Child Pugh classification. Each subject in the moderate hepatic impairment group received a single 30 mg oral dose of apremilast, while a reduced single dose of 20 mg was administered to the severe hepatic impairment group for safety reasons. Safety was also monitored including laboratory tests, ECG, and examination.

For the moderately impaired group, both apremilast and M12 plasma profiles were overall similar in shape, with slightly higher concentrations seen in the healthy subjects. For the severely impaired group, both apremilast and M12 concentrations were again overall similar in shape.

- **Gender**

Study CC-10004-CP-024 was designed to evaluate the effects of age and gender on apremilast exposure after a single dose of 30 mg apremilast in healthy adults. Eligible healthy elderly and young subjects were matched by sex and BMI and received a single apremilast 30 mg tablet under fasting conditions.

Some sex differences in apremilast pharmacokinetics were noted. Both AUC_t and $AUC_{0-\infty}$ were greater in female subjects compared to male subjects by 28% and 31% respectively. T_{max} was 2.75 hours in the female subjects versus 2.5 hours in the male subjects. Apremilast $t_{1/2}$ was also increased by 28% in females compared to males and had a reduced clearance (11.2L/h v 8.57L/h). The sex differences between males and females in terms of apremilast pharmacokinetics were even more pronounced in the elderly population. Apremilast exposure was approximately 30-50% higher in elderly females than in young and elderly males and young females.

Because the overall exposure ($AUC_{0-\infty}$) in elderly and female subjects are within the AUC 0-tau range evaluated at 30mg BID in the phase 2 study (CC-10004-PSOR-005), the effect of gender is considered not to be clinically meaningful.

The effect of gender on the pharmacokinetics of apremilast was also examined in psoriasis patients in one of the pivotal phase 3 clinical studies: CC-1004-PSOR-008-PK. This also revealed an overall reduction in apparent clearance of apremilast in females in the order of 31%. Gender was identified as a statistically significant covariate on apremilast clearance.

- **Race**

The effect of race on pharmacokinetics was examined specifically in one pharmacokinetic study: Study CC-1004-CP-018. A total of 36 healthy subjects were enrolled, 12 subjects from each of the following ethnicities: Japanese, Chinese and Caucasian. The subjects were matched within acceptable limits for age and body mass index. A single dose of either apremilast 20 mg or apremilast 40 mg was compared to placebo. Sequential blood samples were taken up to 48 hours after the dose. $AUC_{0-t,}$ AUC_{0-inf} and C_{max} appear to be dose proportional for both 20 mg and 40 mg single doses for each of the 3 ethnicities studied. The geometric mean $AUC_{0-t,}$ AUC_{0-inf} and C_{max} were in the range of 5.5% to 19.49% less in the Japanese and Chinese groups compared to the White groups.

- **Weight**

Body weight was a statistically significant covariate on apremilast apparent clearance in one population PK analysis, PK-10004-RA-002-PK. Simulations under steady- state with 20mg BD, 30mg BD and 40mg OD regimens of apremilast for the 10^{th} and 90^{th} percentiles for weight were performed in men and women. The subjects with a lower percentile of body weight presented maximum concentrations slightly higher

than subjects with the upper 90th percentile weight, but that the difference was within the expected margin for inter subject variation.

- **Elderly**

Study CC-10004-CP- 024 was designed to evaluate the effects of age and gender on apremilast exposure after a single dose of 30 mg apremilast in healthy adults. With regard to age, t_{max} was comparable between the elderly (mean age 70 +/- 4.15 years), and the younger (mean age 34.3+/-7.17 years) groups at 2.5 hours. AUC exposure was 13% higher in the elderly healthy group compared to the young healthy group (not statistically significant). However the difference was more pronounced when further analysed for gender. Young and elderly females combined had an AUC 30% higher than in young and elderly combined males. AUC was approximately 30-50% higher in elderly females than young and elderly males and young females combined.

Pharmacokinetic interaction studies

- **In vitro**

In vitro studies have been conducted to examine the role of CYP isozymes in the oxidative metabolism of apremilast. The potential inhibitory and inductive effects of apremilast on CYP activities in vitro were also evaluated. In vitro study results demonstrated that apremilast does not inhibit or induce any major CYP450 isozymes (CYP3A4, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP2C8) at clinically-relevant drug levels. These results suggested that when co administered, apremilast is not likely to interact with drugs metabolized by the major CYP450 isozymes and transporters.

Apremilast was also evaluated in vitro as a potential inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3. Additionally apremilast was evaluated as a potential inhibitor of MRP1, MRP2, MRP3, MRP4 and MRP8 in vitro. Apremilast does not inhibit transporters including P-gp, BCRP, OAT1, OAT3, MRP1, MRP2, MRP4, OCT2, OATP1B1, or OATP1B3 at a concentration range of up to at least five times more than the C_{max} of the target clinical dose of 30 mg BID (CC-10004-DMPK-027, CC-10004-DMPK-036, and CC-10004-DMPK-040).

- **In vivo**

Specific interaction studies were carried out for ketoconazole, rifampin, methotrexate and norgestimate (NGM) and ethinyl estradiol (EE).

Ketoconazole Interaction Study- CC-10004-PK-005

The potential for a drug-drug interaction between apremilast and ketoconazole was examined in Study CC-10004-PK-005. The objective of this study was to evaluate the influence of multiple doses of ketoconazole (a known potent CYP3A4 inhibitor and P-gp inhibitor) on the single-dose PK of apremilast. Co-administration with ketoconazole increased apremilast mean AUC by approximately 36% (weak inhibitory effect of ketoconazole) and C_{max} by 5%. The 90% CI of AUC was 126.2% to 147.49%, indicating that this was a statistically significant increase in apremilast exposure.

Rifampin Interaction Study- CC-10004-CP-025

As a strong inducer of CYP3A4, rifampin was specifically studied for drug- drug interactions with apremilast in healthy subjects. Apremilast alone was compared to apremilast administered after multiple oral doses of rifampin, and apremilast delivered with a single IV dose of rifampin. Co-administration

following pre-treatment with multiple once daily oral doses of rifampin increased apremilast apparent clearance from 9.6 L/h to 34.5 L/h, which resulted in a decrease in apremilast mean AUC (approximately 72% lower) and C_{max} (approximately 43% lower) relative to that of apremilast given alone.

Methotrexate Interaction Study- CC-10004-PK-010

Study CC-10004-PK-010 was designed to determine any effect of apremilast on the exposure of methotrexate or its metabolite 7-OH MTX, as well as any potential effect of methotrexate on apremilast exposure on patients on stable doses of weekly methotrexate (10- 20 mg weekly) for the treatment of psoriatic arthritis and rheumatoid arthritis.

Norgestimate (NGM) and ethinyl estradiol (EE) Interaction Study- CC-10004-CP-020

Study CC-10004-CP-020 was designed to evaluate the potential for drug-drug interactions between combined oral contraceptives and apremilast. EE and NGM pharmacokinetic parameters were comparable with and without apremilast treatment.

Exposure relevant for safety evaluation

Safety was examined as a secondary outcome in many of the clinical pharmacology studies. Apremilast appeared to be well tolerated throughout.

Special populations

Table 1: Elderly Subjects Involved in the Apremilast Clinical Program

eCTD Module	Age 65-74 number / total number (all ages)	Age 75-84 number / total number (all ages)	Age 85+ number / total number (all ages)
Efficacy and Safety Studies[a]	361/4089	43/4089	1/4089
Human PK Studies	17/332	5/332	0/332
Human PD Studies	NA	NA	NA
Biopharmaceutical Studies	0/85	0/85	0/85

NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic

[a] Includes subjects in controlled, uncontrolled and other studies. Subjects who were initially randomized to treatment with placebo, and were re-randomized or switched to apremilast are also included.

Source: Table R.3.6, Table R.3.6.2

2.4.3. Pharmacodynamics

Mechanism of action

Apremilast, an oral small-molecule inhibitor of PDE4, works selectively and intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. Apremilast works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cAMP-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines. Elevation of cAMP also modulates anti-inflammatory cytokines, such as IL-10, produced by endotoxin-stimulated mononuclear cells. A reduction in inducible nitric oxide synthase was also observed. These pro- and anti-inflammatory mediators have been implicated in psoriasis and

PsA. In psoriasis studies, apremilast also caused a reduction in the numbers of dendritic cells and T cells infiltrating skin lesions.

Primary and Secondary pharmacology

Primary pharmacology

This has been investigated in studies PSOR-001, PSOR-004, PSA-002 and PSOR-009. In the PSOR studies, APR treatment was associated with a decrease in dendritic cells and T cells infiltrating the skin lesions, within the epidermis or the dermis. Also in both studies, a significant decrease in inducible nitric oxide synthase (iNOS) gene expression was observed in the lesion skin biopsies taken 2, 4, or 12 weeks after treatment initiation. In PSOR-001, a decrease in the ability of whole blood to produce TNF-α in response to endotoxin was observed 2 hours after dosing. PSOR-004 showed that APR decreased lesional skin epidermal thickness and expression of pro-inflammatory genes, including iNOS, IL-12/IL-23p40, IL-23p19, IL-17A, IL-22, and IL-8 while in PSOR-009-PD, changes in inflammatory biomarkers were observed in the peripheral blood at Week 16. Treatment with APR at the proposed therapeutic dose of 30 mg BID also resulted in significantly lower percentage changes from baseline, compared to placebo, of alpha 2 macroglobulin, IL-17, Regulated on Activation, Normal T cell Expressed and Secreted (RANTES) as well as Tissue Inhibitor of Metalloproteinases 1 (TIMP-1) plasma levels. In PSA-002-PD, the only PsA study in which plasma protein biomarkers were examined, APR was associated with modulation of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, TNF-α, matrix metalloproteinase-3 (MMP-3), ferritin, and a small increase in von Willebrand factor (vWF) plasma protein levels (NB. vWF was within the normal range [<120 µg/mL]). Among these, the changes in TNF-α and vWF were significantly associated with achieving an ACR20 clinical response.

Study PSA-002

In this Study PSA-002 a subset underwent PD evaluation. In a total of 150 subjects (placebo: N=51; APR 20 mg BID: N=51; and APR 30 mg BID: N=48) blood samples were taken for biomarker analysis. Of the 51 subjects randomised to treatment with placebo, 18 in the placebo/20 mg group and 14 in the placebo/30 mg group early escaped to active treatment at Week 16. At Week 4, the first post-baseline assessment, a significant ($p<0.05$) effect of APR treatment (20 mg BID or 30 mg BID) compared to placebo was observed in the change and/or percentage change from baseline 4 for IL-8, MCP-1, MIP1-β, MMP-3, and TNF-α. This effect was observed again at Week 16, the primary efficacy endpoint of the clinical trial, for IL-8, MIP-1β, and MMP-3. At Week 16 (LOCF), significant ($p < 0.050$) differences in the change from baseline, or in the percentage change from baseline compared with placebo were observed in the APR 20 BID and/or APR 30 BID groups in IL-8, IL-6, IL-1α, IL-1β, TNF-α, ferritin, and vWF plasma protein levels (CC-10004-PSA-002-PD). At Week 24 (LOCF), subjects in the APR 20 BID or APR 30 BID group had significant ($p < 0.050$) changes compared to subjects treated with placebo in IL- 8, MCP-1, MIP1-β, MMP-3, TNF-α, IL-6, ferritin, IL-2, and vWF plasma protein expression.

Analyses of the within-treatment biomarker changes from baseline over 40 weeks of treatment found that 16 of the 47 analytes (alpha-1 antitrypsin, complement C3, Eotaxin-1, Factor VII, von Willebrand factor, ferritin, IL-10, IL-17, IL-1α, IL-1 receptor antagonist, IL-23, IL-6, IL-8, MIP- 1β, MMP-3, and TNF-α) appeared to show meaningful changes from baseline based upon multiple criteria. Nine of the 16 analytes

showed a statistically significant ($p < 0.05$) percentage change from baseline at Week 40 in the APR 30 mg BID group (Eotaxin-1, Factor VII, Ferritin, IL-10, IL-17, IL-1 receptor antagonist, IL-23, IL-6, MMP-3), including 5 that showed percentage changes that were also significant at Week 40 in the APR 20 mg BID group (Factor VII, IL-1 receptor antagonist, IL-23, IL-6, MMP-3).

PSOR-001

The PD objective of this study was to evaluate the PD effect of orally administered APR (2 X 10 mg once daily [20 mg QD] awakening, when taken for 29 days, for reducing epidermal thickness in subjects with severe plaque PSOR. Eight (53.3%; 95% CI [26.6, 78.7]) of the 15 subjects with evaluable skin biopsies demonstrated
a ≥20% reduction in epidermal thickness at Day 29. Thus, the pre-specified protocol-defined definition of a PD response was met.
Mean reduction from baseline in epidermal and dermal T cells at Day 29 was 18.6% and 23.4%, respectively. Similar changes from baseline in epidermal and dermal CD83 and CD11c cells were observed, although the mean change from baseline was not statistically significant for most parameters. Several subjects with biomarkers present in psoriatic lesional biopsies at baseline showed an absence of these markers at Day 29 (as would be expected in normal, non-psoriatic skin): ICAM-1 and filaggrin, 3 subjects; HLA-DR, 2 subjects; quantitative K16, 1 subject. Mean mRNA gene expression of most psoriasis-related inflammatory markers, including iNOS ($P < 0.0001$) and K16+, was decreased at Day 29 relative to baseline.

APR had a statistically significant inhibitory effect on *ex vivo* whole blood LPS-stimulated TNF-α production 2 hours after the first dose. In the 11 subjects with *ex-vivo* whole blood LPSstimulated TNF-α data, all subjects (11/11) had an inhibition of the LPS-stimulated TNF-α production from predose to 2 hours postdose on Visit 2, whereas 7 out of 11 subjects had the inhibition of the LPS-stimulated TNF-α production from pre-dose to 2 hours post-dose on Visit 6. On Visit 2 (Day 1), the mean % (SD) inhibition of the LPS-stimulated TNF-α was -35.2 % (21.5%), ranging from -71.9% to -5.5% (negative sign indicates inhibition). On Visit 6 (Day 29), the mean % (SD) inhibition of the LPS-stimulated TNF-α production was -5.1% (35.9%), ranging from -43.0% to 79.7%. Inhibition of TNF-α production was also noted after 2 hours post-dose at Day 29 but was not statistically significant, most likely because TNF-α levels were already suppressed from the prior 29 days of therapy. Mean changes in CD19+, CD3+, CD4+, CD8+, and RO±/RA±T-cell subtypes were small with no consistent pattern over time. Interestingly, 12 of 15 subjects experienced a decrease from baseline in the NK (CD16/56+) lymphocyte population at the end of the study drug treatment period compared with pre-treatment (baseline) values. Recent experimental evidence suggests that NK and NK T cells special populations are involved in the pathogenesis of psoriasis as these cells produce INF-γ, which is the only cytokine identified thus far to play a role in psoriasis keratinocyte proliferation (Bos, 2005). Fourteen of the 19 subjects (73.7%) enrolled in the study demonstrated an improvement in their psoriasis symptoms, and 3 (17.6%) of the 17 subjects with data at Day 29 had a > 50% reduction from baseline in their total PASI score (PASI-50). Nine (52.9%) of the 17 subjects with an assessment at Day 29 had at least a 1-category improvement in the

sPGA Average Overall Lesions Scale score relative to baseline. Ten (58.8%) of the 17 subjects with a psoriasis BSA assessment at Day 29 showed an improvement relative to baseline.

Study PSOR-004

In PSOR-004, an open label study in subjects with recalcitrant plaque psoriasis treated with apremilast 20 mg BID, lesional skin biopsies from 20 subjects were evaluated at baseline, Week 4, and Week 12. The intent of the biopsy analysis was to study the extent to which disease-related pathology is affected or impacted by APR and to determine inflammatory pathways which are impacted by its administration in skin lesions of plaque PSOR. This analysis extends a previous analysis in which drug-related effects in PSOR skin lesions were analysed after 4 weeks of treatment (Study PSOR-001). The biopsies were analysed in two ways:

- Histologically- in H&E stained sections of skin biopsies after staining frozen sections of skin biopsies with antibodies to keratin 16, CD3, CD11c, ICAM-1, Langerin, CD56, Foxp3, and HLA-DR, including, therefore assessment of epidermal growth/differentiation, skin infiltration by T-cells and DC subsets, presence of regulatory T-cells, and presence of inflammation-regulating molecules in skin lesions.
- mRNA abundance for a variety of inflammatory molecules-measured by real-time RT-PCR and expression was normalized to the house-keeping gene HARP (human acidic ribosomal protein).

Histological Analysis

Of the 20 cases analysed, 19 showed active PSOR lesions in baseline biopsies.

One Subject had minimally reactive epidermis in the baseline lesional biopsy so did not meet histologic criteria for active psoriasis at baseline biopsy. At Week 4, 10 subjects showed improvement in PSOR based on a reduction in epidermal hyperplasia and/or a reduction in keratin 16 (K16), which is produced only in reactive (hyperplastic) epidermis. Using all measured values of thickness, there was a median 23% reduction in epidermal thickness at Week 4 (P = 0.08 in a 2-sided Wilcoxon signed rank test). Nine subjects showed histological disease improvement in Week 12 biopsies, with 5 subjects showing absence of K16 staining, a marker for hyper-proliferative keratinocytes consistent with plaque PSOR. At this time-point, the median reduction in epidermal thickness was 34% (P = 0.083). Hence, the quantitative reduction in epidermal thickness was not significant for the group as a whole. Since spontaneous improvement in psoriasis is rare, the fact that the 5 subjects became K16- (K16 negative) is clinically meaningful. It was noted that improvement in the disease phenotype was more obvious at Day 29 in some cases and then there appeared to be an increase in PSOR disease activity at Day 85. A summary of changes in histological staining in the dermis and epidermis, as well as epidermal thickness, is provided in Table 20.

Table 20: Summary of Percent Change from Baseline (Week 0) in Histological Parameters from Skin Biopsy by Visit - Safety Population (PSOR-004)

Marker	Location	Week 4	Week 4	Week 12	Week 12
		Median % Change	P value	Median % Change	P value
CD11c	Dermis	-45.8	0.001	-54.6	0.018
	Epidermis	-73.1	0.002	-88.6	0.001
CD3	Dermis	-24.5	0.395	-62.0	0.013
	Epidermis	-35.0	0.018	-47.4	0.074
CD56	Dermis	-27.6	0.246	-12.5	0.632
	Epidermis	-75.6	0.006	-73.3	0.242
Langerin	Dermis	-50.0	0.910	-57.9	0.329
	Epidermis	9.5	0.116	17.1	0.130
Thickness	Epidermis	-22.9	0.080	-34.3	0.083

Source: Table 13 of report CC-10004-PSOR-004

CD11c marks myeloid dendritic cells (DC) in human skin. Normally, there is a resident population of CD11c+ cells in the dermis, but psoriasis shows both an increase in dermal CD11c+ DCs and inappropriate migration of CD11c+ cells into the epidermis of skin lesions. These myeloid DC are also called TIP-DCs (TNF- and iNOS-producing DCs). As to the infiltrating CD11c+ myeloid DCs in these biopsies, overall there was a major reduction in both the dermis and epidermis at both week 4 and week 12. Dermal CD11c+ DCs were reduced in Week 4 and Week 12 biopsies by -45.8% (P=0.001) and -54.6% (P=0.018) respectively. Epidermal CD11c+ DC were reduced to an even greater degree, by -73.1% at week 4 (P=0.002) and -88.6% at week 12 (P=0.001). There were also statistically significant reductions in CD3+ T cells and CD56+ cells (NK cells or NK-T-cells) in the epidermis and dermis. Langerin, a marker of Langerhans cells (LC), was slightly elevated in the epidermis but not the dermis, consistent with normalisation of this cell population with effective therapy. In general, reductions in cellular infiltrates in epidermis and dermis were numerically greater among responders (those with a change in PASI of 75% or more at Week 12) than among non-responders.

The expression of inflammation-associated molecules ICAM-1 and HLA-DR was reduced in parallel with disease improvement reflected by epidermal thickness or K16 staining. These are qualitative markers of inflammation, so the change was not quantified and subjected to statistical analysis. Note that HLA-DR is also expressed by skin-resident DCs, so there was appropriate residual staining for this molecule at Week 12.

To address whether inflammation is suppressed through increase T regulatory (Treg) cell presence in psoriatic plaques, Treg cells were stained. The presence of Treg (Foxp3+) cells in the dermis of skin lesions was reduced over time in parallel with reductions in T-cells.

Gene Expression Analysis of Response

Inflammatory markers assessed by mRNA levels included the chemokine CXCL9, human defensin beta 4 (DEFB4), IFN-γ, IL-10, IL-17a, IL-22, IL-8, K16, Mx-1, IL-12/23 p40, IL-23p19, iNOS, and TNF. These are inflammatory molecules produced by activated DC populations, Th1, Th17, Th22 T-cells, and response genes to interferon (Mx-1, CXCL9) or IL-17 (defensin). Keratin 16 is also measured by mRNA levels to assess the epidermal response by an alternate means. All mRNA levels were normalized to the house-keeping gene HARP (human acidic ribosomal protein).

At Week 12, there was a median reduction in K16 mRNA by 78% (P = 0.015), which is consistent with the overall improvement of PSOR at this same time-point. The reduction in K16 mRNA was of a higher magnitude than the reduction in epidermal thickness, as this keratin is produced only in reactive

(hyperplastic) epidermis. Normal epidermis has a thickness value, so the maximal case for a thickness reduction is to normal values.

From the histologic analysis, CD11c+ myeloid leukocytes showed more consistent reductions than T-cells in lesions. From the genomic standpoint, iNOS, IL-12/IL-23p40, and IL-23p19 genes are products of inflammatory (CD11c+) DCs. Normalized iNOS mRNA expression was reduced by 61% at Week 4 (P = 0.029) and by 100% at Week 12 (P = 0.008). While TNF mRNA level was reduced by 42.7%, this change was not statistically significant; however, it was of sufficient magnitude to elicit clinical response. Another TNF-induced gene in CD11c+ DCs is the IL-12/23 p40 gene. IL-12/23 p40 showed significant reductions in Week 4 and Week 12 biopsies. The expectation of this reduction is that levels of IL-12 and/or IL-23 would be reduced, with subsequent reductions in Th1, Th17, and Th22 T-cell activation, followed by reductions in downstream genes of IL-17 or interferon signaling. IL-17A mRNA levels were reduced by 49% at Week 12 (P = 0.031) and normalized IL-22 mRNA levels were reduced by 100% at Week 12 (P = 0.031). DEFB4 is a defensin-induced in keratinocytes by IL-17. Expression of DEFB4 was reduced by 55% in Week 4 biopsies (P = 0.029) and by 82% in Week 12 biopsies (P = 0.014). IL-8 is also induced in keratinocytes by IL-17. Expression of this inflammatory chemokine was reduced by 76% in Week 4 biopsies (P = 0.004) and by 66% in Week 12 biopsies (P = 0.018). The larger magnitude reduction in IL-8 (as compared to DEFB4), probably reflects the co-regulation of IL-8 by TNF and the fact that TNF signaling is probably reduced by APR. Hence, a strong case can be made that the IL-23/Th17 & Th22 response pathways were reduced in treated skin lesions. From the response pattern, it can also be inferred that TNF signaling (production) is reduced by apremilast. In contrast, there is less evidence that Th1 T-cell activation is strongly affected, as consistent reduction in IFN-γ and CXCL9 mRNA were not measured. However, a consistent reduction in normalised MX-1 mRNA was observed in biopsies: median reduction of 51% at Week 4 (P = 0.008) and a reduction of 52% at Week 12 (P < 0.001).

At the cellular level, pathologic epidermal hyperplasia and production of K16 by epidermal keratinocytes were reduced in Day 29 (Week 4) and Day 85 (Week 12) biopsies. The reduction in K16 mRNA was of higher magnitude than reductions in epidermal thickness, as expected from known biology. One demonstrated action of APR is suppression of TNF mRNA levels in vitro (Schafer, 2010). While a statistically significant reduction in TNF mRNA levels in the skin was not observed in this clinical study, there was a reduction of 42.7%, which was enough to elicit a clinical response. Overall, the results of this study do show a large reduction in inflammatory DCs in psoriasis. CD11c+ DCs in PSOR have also been called TIP-DCs (TNF- and iNOS-producing DCs). APR reduced overall numbers of CD11c+ DCs and, in particular, pathologic infiltration of psoriatic epidermis by this cell set. Reductions in iNOS mRNA and p40 mRNA, along with reductions in Th17 and Th22 T-cell pathways were observed in these psoriasis lesions. From the reductions in MX-1 levels, it is also likely that interferon levels are reduced as a direct or indirect effect of APR. To identify changes in cellular infiltration or gene expression that correlate with changes in PASI score, a correlation analysis was performed using the Spearman rank-order correlation method. A significant correlation was observed between the decrease in CD56+ NK cells in the epidermis and the decrease in the PASI score at week 4 (p = 0.009). A strong trend was observed between the decrease in CD11c+ myeloid DC in the epidermis the decrease in PASI score at Week 4 (p = 0.052). For the inflammatory gene expression, a significant correlation was observed between the decrease in PASI score and the decrease in DEFB4 at Week 4 (p=0.005) and Week 12 (p = 0.009), IL-17A at Week 12 (p = 0.030), K16 at Week 4 (p < 0.001), MX-1 at Week 4 (p = 0.008), and IL-12/IL-23p40 at Week 4 (p = 0.033). These results suggest that K16, MX-1, and IL-12/IL-23p40 mRNA levels may reflect the early effects in the mechanism of action of APR.

PSOR-009

In this randomised, double-blind, placebo-controlled Phase 3 study in subjects with moderate to severe plaque PSOR, PD analysis was carried-out in a subset of 100 out of approximately 405 randomised subjects subjects to explore the relationship of APR to changes in plasma inflammatory biomarkers (47 inflammatory proteins). At selected time points, blood samples for PD analysis were obtained from the subset i.e. at week 0 (baseline), and weeks 4, 16, 32, 36, 40, and 44. In contrast to Studies PSOR-001 and PSOR-004, wherein inflammatory markers were measured in the target tissue, in Study PSOR-009 they were measured in plasma.

At the time of the primary end-point, PASI-75 at Week 16 (last observation carried forward, LOCF), compared to placebo, APR significantly reduced plasma levels of the following proteins: alpha 2 macroglobulin (p=0.0389), an acute phase reactant and coagulation factor overexpressed in psoriasis patients; interleukin-17 (p=0.0454), a key driver of the Th17 immune responses which is central to PSOR pathogenesis; chemokine (CC-motif) ligand 5 (CCL5/RANTES) (p=0.0102), a keratinocyte-derived chemokine which is increased in psoriatic lesional skin, and; tissue inhibitor of metalloproteinase 1 (TIMP-1) (p=0.0073), a Th1 and Th17 cell product that is abundantly expressed in psoriatic skin and plasma. There were no significant associations between changes in these plasma proteins and clinical response as measured by PASI-75 at week 16 (NRI or LOCF).

Secondary pharmacology

Study CC-1004-PK-008 was a randomised, double blinded, placebo controlled trial to determine the potential for apremilast and its major metabolites to affect QT interval. The study was carried out in healthy male subjects. Moxifloxacin was used as an open label positive control to assure the sensitivity of the assay. As the clinically effective dose, 30 mg BD was chosen. A supra-therapeutic dose of 50mg BD was also examined. There were no safety concerns arising from the study. All change from baseline QT values for both the 30 mg BD and the 50mg BD doses were below 1ms, and the upper limit of the 90% CI for both doses was well below 10 ms at all time points.

Relationship between plasma concentration and effect

Study PSOR-005, a Phase 2b dose-ranging study, supports the selection of the apremilast 30mg BD therapeutic dose. In this study, 352 subjects were randomized to 4 treatment groups (placebo, apremilast 10mg BD, 20mg BD, and 30mg BD). The response rates at Week 16 were 11.2% ($p = 0.1846$), 28.7% ($p < 0.0001$), and 40.9% ($p < 0.0001$) for the 10mg BD, 20mg BD, and 30mg BD treatment groups, respectively, compared to the placebo (5.7%). A clear dose response was demonstrated across the doses studied. No clinically significant safety signals were observed in either the 20mg BD or 30mg BD groups.

2.4.4. Discussion on clinical pharmacology

One early study (CC-1004-BA-001) was designed to compare the bioavailabiltyof apremilast capsules made with milled API that of apremilast capsules made with micronized API, under both fasting and fed conditions. In the fasting state AUC and C_{max} for the micronized capsules were significantly higher than for the milled capsules. AUC was 17% less and C_{max} was 22% less in the milled versus the micronized capsules. Also in the fed state C_{max} was significantly higher for the micronized capsules, although AUC was comparable. The applicant stated that these results justify the selection of milled API in the subsequent manufacturing of apremilast tablets. Since milled API was used throughout the clinical

development programme, and in all the pivotal studies, failure to strictly meet BE limits is not clinically significant. This was agreed by the CHMP.

Another early study (CC-1004-BA-002) was designed to compare the bioavailability of apremilast delivered as an oral 40 mg tablet to that of 20 mg apremilast capsules under both fed and fasting conditions. The applicant has concluded that either capsule or tablet formulation could be used in the clinical studies. However in the fasting state the tablet resulted in a 13% increase over capsule formulation for AUC and C_{max}. The 90% CI for the least square mean ratio of tablets to capsules for both C_{max} (96.3;133.88) and AUC (100.16;126.09) lie outside the conventional bioequivalence limits of 80-125%. In the fed state, AUC lay within the conventional limits, however the 90% CI for C_{max} was not (106.96;149.85). Hence the bioequivalence of the tablet to the capsule was not been established. However this study was performed early in the clinical development programme. All of the subsequent major pivotal trials were performed with the milled tablet formulation, hence failure to strictly meet BE limits is not clinically relevant.

CC-10004-RA-002-PK compared apremilast exposure data from healthy subjects with that of patients with rheumatoid arthritis, and showed a 32% reduction in clearance in the RA group. The population PK analyses of cumulative data in healthy subjects and subjects with PsA (studies CC-10004-PSA-001-PK and CC-10004-PSA-002-PK combined) identified that subjects with PsA had approximately 36% slower apremilast clearance than healthy subjects.

In Study CC-10004-PSOR-008-PK a pooled population PK analysis identified disease status and gender as statistically significant covariates on the apparent clearance of apremilast. Overall apparent clearance was 20% slower in patients with psoriasis than in healthy subjects. The apparent clearance of apremilast in subjects with PsA, RA and psoriasis was calculated to be 7.34L/hour, 7.6L/hour and 7.4L/hour respectively. This suggested that each of the inflammatory diseases confers a similar reduction in the apparent clearance of apremilast. By comparison the clearance in healthy volunteers is approximately 10L/hour.

With regards to severe renal impairment (eGFR<30ml/min/1.73m^2), the applicant recommended a reduced dose of 30 mg once daily. This was agreed by the CHMP. Simulations have suggested that 30 mg OD produces apremilast exposure comparable to a 30 mg BD dose in those with normal renal function. A single dose of 30 mg apremilast also appeared to be well tolerated in subjects with severe renal impairment, and their demographically matched subjects with normal renal function.

Pooled population PK analysis from 86 subjects with mild and moderate renal impairment has been provided, and this did not show a correlation between creatinine clearance and apremilast clearance.

The applicant has also provided the results of a subsequent study of apremilast PK in mild and moderate renal impairment that were not available at the time of the original submission, study CC-10004-CP-029. The results of this study, although not statistically significant, supported the findings of the population PK analysis in relation to mild and moderate renal impairment, and also supported the proposal not to dose adjust for patients with mild and moderate renal impairment.

The applicant concluded that there is no evidence to suggest that the pharmacokinetics of apremilast and its major metabolite M12 were affected by moderate or severe hepatic impairment at the doses evaluated in this study, and consequently stated that there need not be dose adjustment for subjects with moderate or severe hepatic impairment. The applicant extrapolated that no remarkable effect would be expected in those with mild hepatic impairment given that no appreciable effect was noted in moderate and severe hepatic impairment. This was agreed by the CHMP. The applicant will provide results of vitro studies to evaluate M12 as an inhibitor of CYP1A2, 2B6, 2C8, 2C9 and 2D6, and as an inducer of CYP2B6 and CYP1A2 (as described in the RMP).

Population PK analysis from a pivotal phase 3 psoriasis study CC-1004-PSOR-008-PK indicated that overall, apparent clearance was approximately 31% lower in female subjects than in males, and that age was not a statistically significant covariate on apparent total plasma clearance. However it is notable that the number of patients included over the age of 75 years was small. The applicant discussed how the increase in drug exposure in female and elderly subjects could result from their smaller mean body weight. Because the overall exposure (AUC0-∞) in elderly and female subjects are within the AUC 0-tau range evaluated at 30mg BID in the phase 2 study (CC-10004-PSOR-005), the effect of gender is considered not to be clinically meaningful. The applicant reported that the exposure differences attributed to gender were within the expected between subject variability for apparent clearance and hence proposed that no dose adjustment based on sex is necessary. This was agreed by the CHMP.

With regard to the effect of race on pharmacokinetics, the applicant has performed analysis based on combined apremilast pharmacokinetic parameters derived from non compartmental analysis in various phase 1 studies in healthy subjects. This has indicated that apremilast exposure is similar among Caucasian, Caucasian Hispanics, non-Caucasian Hispanics and African American ethnicities.

Study CC-10004-PSOR-008-PK which included both healthy subjects and placebo patients, concluded that body weight was not a significant covariate on apremilast clearance, and supported the recommendation that dose adjustment is not required with respect to body weight.

The potential for a drug-drug interaction between apremilast and ketoconazole was examined in Study CC-10004-PK-005. The applicant stated that this is not of clinical relevance based on the 50% to 200% criterion defined a priori in the protocol. Widened confidence intervals were selected on the basis of safety data available for apremilast dosing up to 100mg. The 90% CI of C_{max} was 92.16% to 119.30%, and was within the acceptance range of 80% to 125%. Therefore while ketoconazole did reduce the apparent clearance of apremilast, and increase its AUC by 36%, this does not appear to be clinically meaningful. This was agreed by the CHMP.

Data also showed that that apremilast exposure is decreased when administered concomitantly with strong inducers of CYP3A4 (e.g., rifampicin) and that this may result in reduced exposure. The product information has been updated accordingly and this was agreed by the CHMP.

The data also shown that MTX did not appear to affect apremilast exposure. Apremilast concentrations reached steady state by Day 7, and its parameters were comparable with or without methotrexate, suggesting that methotrexate can be given with apremilast without affecting apremilast exposure. The product information has been updated accordingly and this was agreed by the CHMP.

The data from study CC-10004-CP-020 also shown that that combined oral contraceptives do not affect apremilast exposure. The product information has been updated accordingly and this was agreed by the CHMP.

Study CC-1004-PK-008 was a randomised, double blinded, placebo controlled trial to determine the potential for apremilast and its major metabolites to affect QT interval. The study was carried out in healthy male subjects. All change from baseline QT values for both the 30 mg BD and the 50mg BD doses were below 1ms, and the upper limit of the 90% CI for both doses was well below 10ms at all time points. The CHMP concluded that apremilast is not anticipated to cause any significant prolongation of the QT interval up to the 50mg BD dose.

2.4.5. Conclusions on clinical pharmacology

The absorption, distribution, metabolism and elimination of apremilast have been well characterised.

The effects of gender, age and body weight have been explored in population PK analysis, and the results showed that dose adjustment is not required in each case. While the number of elderly subjects is limited (particularly over 75 years) the analysis showed that any age related reduction in clearance is not clinically significant. Gender and body weight were also examined by means of population PK analysis, and did not emerge as significant covariates.

The recommendation to reduce the dose to 30 mg once daily in severe renal impairment is appropriate. Sufficient data has also been provided to justify the recommendation not to dose adjust in patients with mild and moderate renal impairment.

Drug- drug interactions have been addressed well overall, in particular in relation to the main CYP enzyme involved, CYP3A4. The possibility of interactions in relation to CYP 1A2 and CYP 2A6 has been examined and does appear not to be a concern. There are also studies underway to look at M12 as an inhibitor and inducer of the CYP enzymes (as described in the RMP).

2.5. Clinical efficacy

2.5.1. Dose response studies

The active treatments, 20 mg and 30 mg BID APR, were chosen to be taken forward to Phase 3 on the basis of nonclinical *in vitro* data (reports 5042-107 and 5424-11) and clinical pharmacology data from studies PSA-001-PK and PSOR-005-PK (these study findings indicated that both APR 20 mg and 30 mg BID maintained the level of APR above the half-maximal inhibitory concentration (IC_{50}) for inhibition of the production of the key cytokines in the pathogenesis of PsA (Schafer, 2010) i.e. TNF-α, IL-2, IL-8, IL-12, interferon-gamma (IFN-γ), and MCP-1) and two Phase 2 trials (Study PSA-001 in PsA and Study PSOR-005 in PSOR).

Within the clinical development programme, two Phase 2 trials (PSA-001 and PSOR-005) assessed the efficacy and safety in PsA, compared to placebo, of APR 20 mg BID and 40 mg QD (once daily) over a 12 week period. On 20 mg active treatment, separation from placebo was seen as early as Week 4, with a statistically significantly greater proportion of subjects on active treatment achieving an ACR 20 and ACR 50 response at Week 12. ACR 20 was 43.5% versus 11.8%; p <0.001 and ACR 50 was 17.4% versus 2.9%; p = 0.012 on active and placebo, respectively. In contrast, the APR 40 mg QD treatment group achieved statistical significance, compared with placebo for only ACR 20 (35.8% versus 11.8%; p = 0.002) and not for ACR 50 (13.4% versus 2.9%; p=0.056 for active and placebo, respectively. Safety and tolerability was comparable between the two dosing regimens. Based on these findings, i.e. greater efficacy with comparable safety and tolerability, BID dosing was selected over QD dosing for the Phase 3 programme.

In the Phase 2 study (PSOR-005) in subjects with moderate to severe PSOR a clear dose response was seen comparing 10, 20 and 30 mg BID. The primary endpoint of the study, the proportion of subjects achieving a 75% or greater improvement in the Psoriasis Area and Severity Index (PASI-75 response) at Week 16, was not seen at the 10 mg BID level but was statistically significant with both 20 and 30 mg BID (28.7% and 40.9%, respectively, compared to 5.7% for placebo; p < 0.0001 for both comparisons). Separation of the PASI-75 response between the active and placebo arms was seen by Week 4 with 30 mg BID but was slower, being seen at Week 8, with the lower 20 mg dose.

Apremilast was well tolerated at both doses, with no clinically important emergent safety signals and a comparable safety profile. For both dose levels the Cmin exceeded the IC50 for inhibition of the production of multiple PDE4-dependent cytokines (Schafer, 2010). Given the genetic and immunologic association between psoriasis and PsA, the applicant considered it was reasonable to extrapolate from these data in psoriasis and assume that a similar safety and efficacy profile would also apply to the PsA population also.

Based on these findings, it was decided that 20 mg and 30 mg APR BID would be compared in Phase 3 for PSA and 30mg BID was used for PSOR. This was agreed by the CHMP.

2.5.2. Main studies

PSORIATIC ARTHRITIS

The Apremilast clinical development program for the treatment of psoriatic arthritis comprises one Phase 2 study (Study PSA 001) and four Phase 3 studies (PSA-002, PSA-003, PSA 004 and PSA-005).

Studies PSA-002, PSA-003, and PSA-004 evaluated apremilast as a monotherapy or in combination with small-molecule DMARDs, and Study PSA-005 evaluated apremilast as a monotherapy. Studies PSA-002, PSA-003, and PSA-004 are ongoing and are considered pivotal to the proposed indication. The 24-week placebo-controlled phase and the active-treatment phase up to Week 52 have been completed in each of these studies. The studies are currently continuing in the active-treatment/long-term safety phase. Data up to 52 weeks for these studies are included in this application. Data up to 24 weeks are described for Study PSA-005.

Study PSA-002 (PALACE 1): A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis.

Study PSA-003 (PALACE 2): A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis.

Study PSA-004 (PALACE 3): A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis and a qualifying psoriasis lesion.

Study PSA-005: A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis who have not been previously treated with disease-modifying antirheumatic drugs.

Methods

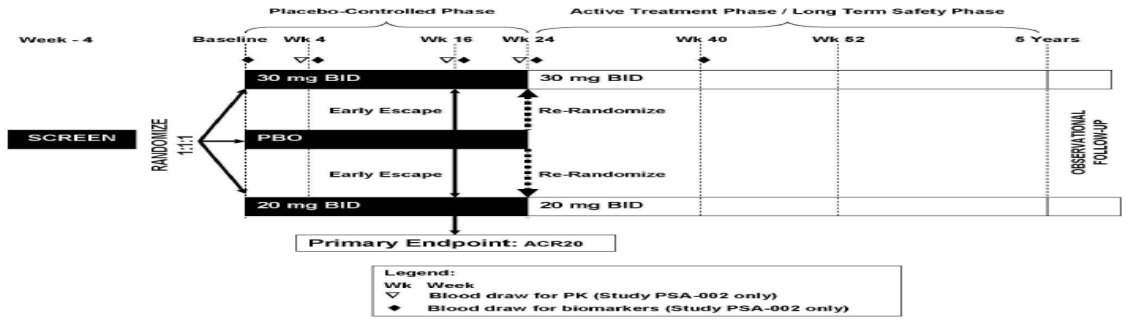
Each of these studies has a common, replicate, design which includes three treatment phases (Figure 1):

- Treatment Phase 1: 24-weeks, randomised, double-blind, placebo-controlled
- Treatment Phase 2: randomised, double-blind active treatment phase of at least 28 weeks' duration,
- Treatment Phase 3: open-label, long-term safety phase of up to 4 years' duration.

The overall study duration of each study is 5 years.

An early escape provision was included in the study design. At Week 16 (the time of the primary endpoint), all subjects whose TJC and SJC had both not improved by 20% were required to enter early escape (EE) to blinded active treatment. Subjects in the APR 20 BID and APR 30 BID treatment groups who met EE criteria continued to receive the same dose of apremilast to which they were originally assigned, under blinded conditions. At Week 24, all subjects in the placebo group who had not entered EE at Week 16 were rerandomized 1:1 in a blinded fashion to receive 20 mg BID or 30 mg BID apremilast (PBO/20 crossover [XO] and PBO/30 XO treatment groups, respectively). Subjects who were already receiving apremilast at Week 24 (i.e., those who were initially randomized to apremilast or who had entered EE at Week 16) continued to receive their randomized treatments in a blinded fashion.

Figure 1 - Study Design Schematic (Studies PSA-002, PSA-003, PSA-004, PSA-005)



ACR 20 = modified American College of Rheumatology 20% response; BID = twice daily; PBO = placebo; PK = pharmacokinetics
Note: Subjects who prematurely discontinued immediately entered the 4-week post-treatment observational follow-up period.

Study Participants

To be eligible for inclusion, subjects had to have a documented diagnosis of PsA (by any criteria) of ≥ 6 months' duration in the pivotal Phase 3 studies (PSA-002, PSA-003, PSA-004) or ≥3 months' duration in Study PSA-005. In addition, in all four studies, subjects were required to meet CASPAR criteria at screening and have active disease, as evidenced by ≥3 swollen and ≥3 tender joints. All subjects in Study PSA-004 also had to have at least one qualifying psoriasis skin lesion ≥2 cm in addition to active PsA, and subjects were stratified by baseline body surface area (BSA).

The eligibility criteria for the pivotal Phase 3 studies (PSA-002, PSA-003, and PSA-004) required subjects to have been treated with small-molecule and/or biologic DMARD(s). The enrolment of subjects with therapeutic failure to TNF blockers was limited to 10%. All subjects who had been on a small-molecule DMARD (or combination DMARDs) for at least 4 months and were taking a stable dose for at least 4 weeks prior to screening, were permitted to continue concurrent small-molecule DMARD(s) treatment (MTX, LEF, and/or SSZ). Across the three PsA Phase 3 studies, approximately 65% (966/1493) of subjects were taking permitted DMARDs (MTX, LEF, and/or SSZ) at baseline, with a median treatment duration of 21.8 months and 15.1 months on a stable dose. 96.2% (929/966) of subjects had at least 4 months of continuous exposure at baseline. 75% of patients on DMARD were treated with methotrexate (MTX) and on average were treated with MTX for 21 months and on a stable dose for 14 of those months. The average dose of MTX was 15mg. Concomitant treatment with biologics, including TNF blockers, was prohibited. Treatment assignments were stratified based on small-molecule DMARD use at baseline (yes/no) and, in Study PSA-004, by baseline BSA involvement with psoriasis (<3% and ≥ 3%). Subjects who had previously failed treatment with >3 agents for PsA (small molecules and/or biologics) or >1 biologic TNF blocker were excluded.

Treatments

Subjects were randomised to receive apremilast 20 mg BID (APR 20 BID treatment group), apremilast 30 mg BID (APR 30 BID treatment group), or identically placebo during the 24-week placebo-controlled phase. As for the PSOR programme, apremilast was dose-titrated in 10-mg/day increments over the first week of treatment. In accordance with the titration schedule, subjects in the APR 20 BID treatment group reached their target dose on Day 4 of treatment, and subjects in the APR 30 BID treatment group reached their target dose on Day 6 of treatment.

Objectives

The primary objective of all 4 studies was to evaluate the clinical efficacy of 2 doses of apremilast (20 mg or 30 mg orally twice daily [BID]), compared with placebo, on the signs and symptoms of PsA after 16 weeks' administration.

Secondary Objectives

1. To evaluate the following in subjects with active PsA who are treated with 2 doses of apremilast or placebo for up to 24 weeks:

- Safety and tolerability

- Efficacy

- Physical function

- Fatigue

- Clinical disease activity

2. To evaluate the following in subjects with active PsA who are treated with 2 doses of apremilast for up to 52 weeks:

- Safety and tolerability

- Efficacy

- Physical function

- Fatigue

- Clinical disease activity

- To evaluate the efficacy, safety, and tolerability of 2 doses of apremilast during up to 5 years' administration to subjects with active PsA

Study 004 also included evaluation of psoriatic skin lesions as a secondary objective. Study 002 also included a pharmacokinetic (PK) and pharmacodynamic (PD) sub study.

Outcomes/endpoints

The primary endpoint was the proportion of subjects in each apremilast treatment group (APR 20 BID and APR 30 BID), compared with placebo, who achieved a modified ACR 20 response after 16 weeks of therapy. The modified ACR 20 required at least 20% improvement, relative to baseline, in both TJC and SJC, as well as at least 20% improvement, relative to baseline, in at least 3 of the 5 following components:

- HAQ-DI Patient's (subject's) global assessment of disease activity

- (PGA) Subject's assessment of pain
- Evaluator's (physician's) global assessment of disease activity (EGA)
- C-reactive protein (CRP)

Other ACR response assessments, ACR 50 and ACR 70, were similarly defined, except that 50% and 70% improvements from baseline, respectively, were required. Change from Baseline in HAQ-DI at Week 16 was the key secondary endpoint.

An extensive range of secondary endpoints have been evaluated in this application at week 24 and 52 including PsARC, CDAI, EULAR, SF-36 (Physical function Domain score and Physical Component Summary) FACIT-F, MASES, Dactylitis Severity Score, BASDAI and PASI-75.

Sample size

Sample size estimations were based on the results of the phase 2 Study PSA-001. A 2-group chi-square test with a 0.025 two-sided significance level has more than 95% power to detect a true 20% absolute difference (40% versus 20%) between one dose of apremilast and placebo, for the proportion of subjects achieving an ACR 20 when the sample size in each group is 165.

Randomisation

At the Baseline Visit (Week 0), subjects who met the inclusion/exclusion criteria were randomized in parallel in a 1:1:1 ratio to receive either 20 mg BID or 30 mg BID apremilast or placebo, using the IVRS. The IVRS stratified the randomization according to DMARD treatment (yes/no) and ensured that at least 25 subjects in the DMARD treated group were taking either LEF or SSZ. Placebo subjects who did not experience ≥20% improvement in SJC and TJC by Week 16 (i.e., met early escape (EE) criteria were required to transition early to active treatment and were re-randomized 1:1 in a blinded fashion to apremilast 20 mg BID or 30 mg BID. Subjects on active treatment who met EE criteria continued to receive, in a blinded fashion, the same dose of apremilast to which they were originally assigned. After 24 weeks of treatment, all of the subjects in the placebo group who had not entered EE at Week 16 were to be re-randomized 1:1 to receive 20 mg BID or 30 mg BID of apremilast, again stratified for DMARD use (yes/no).

Blinding (masking)

Blinding to treatment assignment was maintained at all study sites until after the Week 52 database lock at Year 1, after all final analyses were completed and the final results were released. At that time, open-label study medication was to be provided. Subjects who were receiving apremilast at Week 24 (i.e., those who were originally randomized to the APR 20 BID or APR 30 BID treatment groups, and those who entered EE at Week 16) continued to receive their randomized apremilast treatments in a blinded fashion.

Statistical methods

The evaluation of efficacy of apremilast was based on the results from the individual studies. Efficacy endpoints were analyzed at both the Week 16 (the timing of the primary endpoint) and Week 24 time points during the placebo-controlled period for each individual study. Handling of early escape at Week 16 and missing values at Week 16 and Week 24 was consistent for all four studies. The statistical methods were identical in each of the studies with the exception of adjustment for stratification factors. In the three pivotal Phase 3 studies only (PSA-002, PSA-003, and PSA-004), the treatment comparisons were adjusted for strata of baseline DMARD use (yes/no) and baseline BSA involvement with psoriasis (<3% and ≥3%; the latter for Study PSA-004 only). The secondary endpoints at Weeks 16 and 24 in Studies

PSA-002, PSA-003, PSA-004, and PSA-005 were analyzed in a hierarchical fashion to control the Type I error rate, as outlined in the studies' statistical analysis plans.

Results

Participant flow

There were 1493 subjects randomised and treated across the 3 pivotal studies and are included in the FAS (496 placebo, 500 APR 20 BID, 497 APR 30 BID) (Table 21).

Disposition of Subjects During the Placebo-controlled Phase (Weeks 0-24)

The disposition of subjects during the placebo-controlled phase (Weeks 0-24) of the pivotal Phase 3 studies was generally comparable across treatment groups and across the individual Studies. In the pooled analysis, the majority (92.9%) of subjects in the pivotal Phase 3 studies completed Week 16 (the time of the primary endpoint) (93.1%, 93.2%, and 92.4% in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively). The most frequently cited reasons for study discontinuation prior to Week 16 were AEs (2.8%, 3.0%, and 5.0% of subjects in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively), withdrawal by subject (1.6%, 1.8%, and 0.8%, respectively), and lack of efficacy (1.4%, 1.4%, and 0.8%, respectively).

The proportion of subjects entering EE at Week 16 decreased in a treatment- and dose-dependent manner (58.9%, 42.6%, and 35.2% of subjects in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively).

Table 21: Subject Disposition During the Placebo-Controlled Phase (Weeks 0-24) (Pooled Analysis; FAS)

	Number (%) of Subjects			
Subjects Who:	**Placebo N = 496**	**APR 20 BID N = 500**	**APR 30 BID N = 497**	**Total N =1493**
Received at least 1 dose of IP	496 (100.0)	500 (100.0)	497 (100.0)	1493 (100.0)
Completed Week 16 visit	**462 (93.1)**	**466 (93.2)**	**459 (92.4)**	**1387 (92.9)**
Completed Week 16 and continued[a]	447 (90.1)	447 (89.4)	438 (88.1)	1332 (89.2)
Completed Week 16 but did not continue[b]	15 (3.0)	19 (3.8)	21 (4.2)	55 (3.7)
Early escaped at Week 16	**292 (58.9)**	**213 (42.6)**	**175 (35.2)**	**680 (45.5)**
Discontinued prior to Week 16	34 (6.9)	34 (6.8)	38 (7.6)	106 (7.1)
Primary reason for discontinuation				
Adverse event	14 (2.8)	15 (3.0)	25 (5.0)	54 (3.6)
Lack of efficacy	7 (1.4)	7 (1.4)	4 (0.8)	18 (1.2)
Noncompliance with study drug	0	0	1 (0.2)	1 (0.1)
Withdrawal by subject	8 (1.6)	9 (1.8)	4 (0.8)	21 (1.4)
Death	0	1 (0.2)	0	1 (0.1)
Lost to follow-up	1 (0.2)	0	1 (0.2)	2 (0.1)
Protocol violation	1 (0.2)	0	2 (0.4)	3 (0.2)

Other	3 (0.6)	2 (0.4)	1 (0.2)	6 (0.4)
Completed the Placebo-Controlled Phase (Week 24 visit)	**439 (88.5)**	**436 (87.2)**	**435 (87.5)**	**1310 (87.7)**
Discontinued prior to Week 24	57 (11.5)	64 (12.8)	62 (12.5)	183 (12.3)
Primary reason for discontinuation				
Adverse event	25 (5.0)	25 (5.0)	30 (6.0)	80 (5.4)
Lack of efficacy	13 (2.6)	12 (2.4)	13 (2.6)	38 (2.5)
Noncompliance with study drug	0	1 (0.2)	2 (0.4)	3 (0.2)
Withdrawal by subject	12 (2.4)	18 (3.6)	7 (1.4)	37 (2.5)
Death	0	1 (0.2)	0	1 (0.1)
Lost to follow-up	2 (0.4)	1 (0.2)	5 (1.0)	8 (0.5)
Protocol violation	1 (0.2)	1 (0.2)	2 (0.4)	4 (0.3)
Other	4 (0.8)	5 (1.0)	3 (0.6)	12 (0.8)

APR = apremilast; BID = twice daily; FAS = full analysis set; IP = investigational product.
[a] Includes subjects who had a Week 16 visit and IP dispensed at the visit.
[b] Includes subjects who had a Week 16 visit but IP was not dispensed at the visit, or who did not have a Week 16 visit but discontinued on a date no earlier than the visit window for Week 16 (± 7 days).

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Source: Table 1.2.1 and Table 1.2.2.

Disposition of Subjects During the Active-Treatment/Long-term Safety Phase (Weeks 24-52)

There was some variability across the pivotal Phase 3 studies with regard to the disposition of subjects during Weeks 24-52. However, the trends observed across the treatment groups were generally consistent with the pooled analyses. In subjects initially randomised to apremilast who entered the Week 24-52 study period, the proportions of subjects completing Week 52 were comparable between the APR 20 BID and APR 30 BID treatment groups (89.6% and 88.7%, respectively).

The most frequently reported reasons for discontinuation in the APR 20 BID and APR 30 BID treatment groups were lack of efficacy (3.9% and 4.6%, respectively), withdrawal by subject (3.4% and2.6%, respectively), and AEs (2.4% in both groups).

Overall Disposition of Subjects (Weeks 0-52)

The overall rates of completion of Weeks 0-52 in subjects initially randomised to the APR 20 BID and APR 30 BID treatment groups were 73.8% (369/500) and 74.4% (370/497), respectively. Additionally, 73.2% (363/496) of subjects randomised to the placebo group completed Weeks 0-52 (this included 111 subjects in the PBO/20 EE group, 112 subjects in the PBO/30 EE group, 67 subjects in the PBO/20 XO group, and 73 subjects in the PBO/30 XO treatment group). These overall completion rates were consistent with the completion rates in the individual pivotal Phase 3 studies.

Recruitment

PSA-002: First subject enrolled: 2nd June 2010; Week 52 completed 2nd October 2012

PSA-003: First subject enrolled: 27th September 2010; Week 52 completed 27th December 2012.

PSA-004: First subject enrolled: 30th September 2011; Week 52 completed 28th January 2013.

PSA-005: First enrolment 9th December 2010; Week 24 completed 14th January 2013.

Conduct of the study

All three studies had 6 protocol amendments the most significant of which was Protocol Amendment 6 (03 July 2012) where the assessment of the primary efficacy endpoint (ACR 20) was made at Week 16 instead of Week 24. Study PSA005 had 5 protocol amendments were implemented including extending blinded treatment duration with apremilast from 12 weeks to 24 weeks.

Baseline data

Comparison of populations in Studies PSA 002, PSA003 and PSA004

The demographic characteristics of subjects at baseline were generally well-balanced across the studies PSA002, PSA003 and PSA004 treatment groups. There was some minor variability across the study populations with a higher proportion of female subjects in two of the three studies (PSA-003 (57%) and PSA-004 (53%) and the distribution of subjects by geographic region varied across the three pivotal Phase 3 studies. Otherwise in terms of demographic characteristics the three studies were generally similar.

	North America	Europe	Rest of the world
PSA002	44.2%	24.2%	31.5%
PSA003	24%	64%	12%
PSA004	32.5%	45.9%	21.6%

Pooled analysis

When pooling Studies PSA002, 003 and 004 the FAS comprised 1493 patients; 496 in the placebo group and 500 in the APR20mg BID group and 497 in the APR30mg BID group.

The majority of subjects enrolled in this study were white (93.6%) and 53.5% of all subjects were female; the mean age was 50.3 years, and the mean weight was 85.65 kg (mean body mass index [BMI] was 29.94 kg/m2). In the pooled analysis, the greatest proportion of subjects were from Europe (44.5% versus 33.7% from North America and 21.8% from the rest of the world).

The disease history of subjects was generally well-balanced across treatment groups in the three studies and the pooled analysis. The proportion of patients with predominant spondylitis 32/1439 (2.1%) reflects the relative proportion of patients with this PsA subtype within the general PsA population. In the predominant spondylitis subgroup 3/12 (25%) of APR30mg BID vs 2/7 (28.6%) placebo had a treatment effect in favour of placebo.

Baseline Disease History (FAS) pooled analysis

Disease Characteristic	Placebo N = 496	APR 20 BID N = 500	APR 30 BID N = 497	Total N = 1493
Duration of PsA (years since diagnosis)				
Mean ± SD	7.27 ± 7.292	7.58 ± 7.732	7.47 ± 7.784	7.44 ± 7.602
Median (min – max)	5.25 (0.1 – 54.4)	4.70 (0.2 – 41.3)	4.80 (0.4 – 57.3)	5.00 (0.1 – 57.3)
PsA type, n (%)				
Symmetric polyarthritis	298 (60.1)	319 (63.8)	309 (62.2)	926 (62.0)
Asymmetrical oligoarthritis	138 (27.8)	127 (25.4)	136 (27.4)	401 (26.9)
Predominant DIP involvement	34 (6.9)	31 (6.2)	28 (5.6)	93 (6.2)
Arthritis mutilans	18 (3.6)	10 (2.0)	12 (2.4)	40 (2.7)
Predominant spondylitis	7 (1.4)	13 (2.6)	12 (2.4)	32 (2.1)
History of psoriasis (diagnosis)				
Yes	494 (99.6)	499 (99.8)	492 (99.0)	1485 (99.5)
No	1 (0.2)	1 (0.2)	3 (0.6)	5 (0.3)
Missing	1 (0.2)	0	2 (0.4)	3 (0.2)
Duration of psoriasis (years since diagnosis)				
n	494	499	492	1485
Mean ± SD	17.11 ± 13.410	17.21 ± 13.528	17.39 ± 13.003	17.24 ± 13.308
Median (min – max)	13.65 (0.0 - 62.0)	14.20 (0.2 - 64.8)	14.70 (0.0 - 58.4)	14.20 (0.0 - 64.8)
Psoriasis history,[a] n (%)				
Guttate, pustular, or erythrodermic psoriasis	7 (1.4)	7 (1.4)	10 (2.0)	24 (1.6)
Palmoplantar psoriasis	65 (13.1)	64 (12.8)	47 (9.5)	176 (11.8)
Plaque-type psoriasis	375 (75.6)	374 (74.8)	385 (77.5)	1134 (76.0)
Nail psoriasis	328 (66.1)	323 (64.6)	348 (70.0)	999 (66.9)
Scalp psoriasis	384 (77.4)	399 (79.8)	387 (77.9)	1170 (78.4)

Baseline Disease Characteristics

Baseline disease activity, per the ACR component scores, was consistent with a subject population with active PsA. The mean (median) TJC was 21.0 (16.0) and the mean (median) SJC was 11.3 (9.0), and was consistent across treatment groups. Subjects had impaired physical function, as indicated by mean (median) HAQ-DI score of 1.178 (1.250). There was consistency observed across the VAS assessment scores for the mean (median) subject's assessment of pain (56.8 [58.5]), PGA (56.2 [58.0]), and EGA (54.8 [55.0]). Other baseline disease activity measures, including the SF-36v2 physical functioning domain, CDAI, DAS28 (CRP), FACIT-Fatigue, MASES, and Dactylitis severity scores, were likewise indicative of a subject population with active PsA, and these were generally well-balanced across treatment groups in the pooled analysis and across the three pivotal Phase 3 studies.

Numbers analysed

PSA-002

Table 23 - Number of Subjects Included in Data Sets Analyzed

Data Set	Treatment Group			Total
	Placebo	APR 20 BID	APR 30 BID	
Full analysis set (FAS)	168	168	168	504
PP Population	165	163	161	489
AAR Population	PBO/APR 20 BID EE: 54 PBO/APR 20 BID XO: 23 PBO/APR 30 BID EE: 53 PBO/APR 30 BID XO: 24	Total randomized[a]: 168 APR 20 BID EE: 78 APR 20 BID NEE: 74	Total randomized[a]: 168 APR 20 BID EE: 58 APR 20 BID NEE: 91	490

AAR = apremilast subjects as randomized/re-randomized; APR = apremilast; BID = twice daily; EE = early escape (re-randomized to apremilast at Week 16); NEE = no early escape after completing Week 16 visit; PBO = placebo; XO = crossover (re-randomized to apremilast at Week 24).PP = per-protocol.
a Total randomized includes subjects who discontinued prior to Week 16 and are therefore not included in the EE and NEE groups.

PSA-003

Table 24: Number of Subjects Included in Data Sets Analyzed

Data Set	Treatment Group			Total
	Placebo	APR 20 BID	APR 30 BID	
Full analysis set (FAS)	159	163	1 6 2	484
PP Population	154	159	1 5	464
AAR Population	PBO/APR 20 BID EE: 44 PBO/APR 20 BID XO: 27 PBO/APR 30 BID EE: 44 PBO/APR 30 BID XO: 28	Total randomized[a]: 163 APR 20 BID EE: 59 APR 20 BID NEE: 87	Total randomized[a]: 162 APR 30 BID EE: 64 APR 30 BID NEE: 79	468

AAR = apremilast subjects as randomized/re-randomized; APR = apremilast; BID = twice daily; EE = early escape (re-randomized to apremilast at Week 16); NEE = no early escape after completing Week 16 visit; PBO = placebo; XO = crossover (re-randomized to apremilast at Week 24); PP = per-protocol.
[a] Total randomized includes subjects who discontinued prior to Week 16 and are therefore not included in the EE and NEEgroups.

PSA-004

Table 25: Number of Subjects Included in Data Sets Analyzed

Data Set	Treatment Group			Total
	PBO	APR 20 BID	APR 30 BID	
FAS	169	169	167	505
PP Population	164	163	159	486
AAR Population	PBO/APR 20 BID EE: 47 PBO/APR 20 BID XO: 25 PBO/ARP 30 BID EE: 50 PBO/APR 30 BID XO: 25	Total randomized[a]: 169 APR 20 BID EE: 76 APR 20 BID NEE: 73	Total randomized: 167 APR 30 BID EE: 53 APR 30 BID NEE: 95	483

AAR = apremilast subjects as randomized/re-randomized; APR = apremilast; BID = twice daily; EE = early escape (re-randomized to apremilast at Week 16); FAS = full analysis set; NEE = no early escape after completing Week 16 visit; PBO = placebo; XO = crossover (re-randomized to apremilast at Week 24); PP = per-protocol.

[a] Total randomized includes subjects who discontinued prior to Week 16 and are therefore not included in the EE and NEE groups.

PSA-005

Table 26: Number of Subjects Included in Data Sets Analyzed

Data Set	Treatment Group			Total
	Placebo	APR 20 BID	APR 30 BID	
Full Analysis Set	176	175	176	527
Per-Protocol Population	166	168	167	501

APR = apremilast; BID = twice daily.

Outcomes and estimation

- **Reduction of Signs and Symptoms**

Primary endpoint (ACR 20 Response at Week 16)

Table 27: Primary Endpoint: Proportion of Subjects Achieving a Modified ACR 20 Response at Week 16 in Studies PSA-002, PSA-003, and PSA-004 (FAS; NRI)

Study	Placebo	APR 20 BID			APR 30 BID		
	n/N (%)[(a)]	n/N (%)[a]	Trt. Effect	P-value	n/N (%)[a]	Trt. Effect	P-value
PSA-002	32/168 (19.0)	51/168 (30.4)	11.3	**0.0166**	64/168 (38.1)	19.0	**0.0001**
PSA-003	30/159 (18.9)	61/163 (37.4)	18.7	**0.0002**	52/162 (32.1)	13.4	**0.0060**
PSA-004	31/169 (18.3)	48/169 (28.4)	9.8	**0.0295**	68/167 (40.7)	22.3	< **0.0001**

ACR 20 = American College of Rheumatology 20% response; APR = apremilast; BID = twice daily; FAS = full analysis set; NRI = nonresponder imputation; Trt. = treatment.

[(a)] Subjects who discontinued early prior to Week 16 and subjects who did not have sufficient data for a definitive determianation of responses status at Week 16 were counted as nonresponders. Joints temporarily or permanently not assessable at baseline were excluded from joint count. For other unassessed joints at baseline, the joint assessment at the Screening visit, if assessed, was used as the Baseline assessment; otherwise, the joint was excluded from joint count.The last observed joint assessment (at baseline or postbaseline) was used for joints unassessed at Week 16. There was no imputation for other missing ACR component scores.

Table 28: Proportion of Subjects Achieving A Modified ACR 20 Response at Weeks 16 and 24 (Pooled Analysis; FAS; NRI)

	Placebo N = 496	APR 20 BID N = 500			APR 30 BID N = 497		
Visit	n (%)	n (%)	Trt. Effect[a]	P-value[b]	n (%)	Trt. Effect[a]	P-value[b]
Primary Endpoint							
Week 16	93 (18.8)	160 (32.0)	13.2	*<0.0001*	184 (37.0)	18.3	*<0.0001*
Week 24	73 (14.7)	139 (27.8)	13.0	*<0.0001*	151 (30.4)	15.8	*<0.0001*

ACR 20 = American College of Rheumatology 20% response; APR = apremilast; BID = twice daily; FAS = full analysis set; NRI = nonresponder imputation.

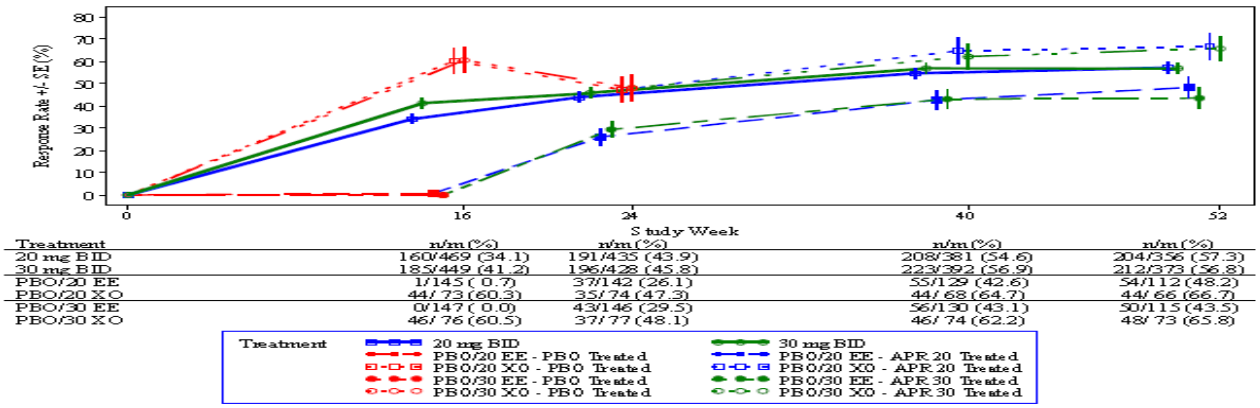
[a] Treatment effect is based on adjusted difference in proportions for apremilast versus placebo (weighted average of the treatment differences across the strata of baseline disease-modifying antirheumatic drug [DMARD] use and study with the Cochran-Mantel-Haenszel [CMH] weights).

[b] 2-sided P-value is based on Cochran-Mantel-Haenszel test adjusting for baseline disease-modifying antirheumatic drug (DMARD) use and study. P-values in italics for the pooled analysis are ≤ 0.050 and considered nominally significant as there was no adjustment for multiplicity.

Apremilast-exposure Period (Weeks 0-52)

In all three pivotal Phase 3 studies, the analysis of the modified ACR 20 in the AAR Population (using data as observed) was supportive of the results presented above for the FAS (using NRI) outlined above. Response rates generally improved between Weeks 24 to 52 of treatment in subjects initially randomized to the APR 20 BID and APR 30 BID treatment groups, based on the data available at each visit (see Figure 2 below for the pooled analysis). At Week 52, the modified ACR 20 response rates observed in the APR 20 BID and APR 30 BID treatment groups were generally comparable, ranging from 52.9% to 63.0% in the APR 20 BID treatment group and from 52.6% to 63.0% in the APR 30 BID treatment group across the three studies. Placebo subjects who did achieve a ≥ 20% improvement in TJC and SJC at week 16 continued to receive placebo until Week 24, at which time they were switched to apremilast (PBO/20 XO and PBO/30 XO groups). These patients showed a high placebo response at Week 16, particularly for the modified ACR 20, which started to decline by Week 24 but consistently outperforms both APR treatment groups across all three studies and the in the pooled analysis.

Figure 2 - Proportion of All Subjects Exposed to Apremilast Achieving Modified ACR 20 Responses During the Apremilast-exposure Period up to Week 52 (AAR Population; Pooled Studies PSA-002, PSA-003 and PSA-004; Data as Observed)



Treatment	n/m (%)	n/m (%)	n/m (%)	n/m (%)
20 mg BID	160/469 (34.1)	191/435 (43.9)	208/381 (54.6)	204/356 (57.3)
30 mg BID	185/449 (41.2)	196/428 (45.8)	223/392 (56.9)	212/373 (56.8)
PBO/20 EE	1/145 (0.7)	37/142 (26.1)	55/129 (42.6)	54/112 (48.2)
PBO/20 XO	44/ 73 (60.3)	35/ 74 (47.3)	44/ 68 (64.7)	44/ 66 (66.7)
PBO/30 EE	0/147 (0.0)	43/146 (29.5)	56/130 (43.1)	50/115 (43.5)
PBO/30 XO	46/ 76 (60.5)	37/ 77 (48.1)	46/ 74 (62.2)	48/ 73 (65.8)

Improvement in Physical Function

Key Secondary Endpoint (Change from Baseline in HAQ-DI at Week 16)

Change from Baseline in HAQ-DI at Week 16 was identified as a key secondary endpoint. Statistically significant improvement (reduction) from baseline in the HAQ-DI score at Week 16 (the key secondary endpoint) was seen in the APR 30 BID treatment group in all three pivotal Phase 3 studies and in the APR 20 BID treatment group in two studies (PSA-002 and PSA-003).

Table 29 - Change from Baseline in the HAQ-DI Score at Weeks 16 and 24 (Pooled Analysis; FAS; LOCF)

Visit Treatment Group	n[a]	Baseline Mean	LS Mean (SE)[b] Change from Baseline	Treatment Comparison	
				LS Mean Difference[b]	P-value[b]
Key Secondary Endpoint **Week 16**					
Placebo	481	1.172	-0.068 (0.0202)	--	--
APR 20 BID	485	1.135	-0.162 (0.0202)	-0.094	0.0009
APR 30 BID	473	1.204	-0.211 (0.0203)	-0.143	< 0.0001
Week 24					
Placebo	481	1.172	-0.071 (0.0210)	--	--
APR 20 BID	486	1.133	-0.171 (0.0210)	-0.100	0.0006
APR 30 BID	476	1.206	-0.219 (0.0211)	-0.148	< 0.0001

APR = apremilast; BID = twice daily; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire Disability Index; LOCF = last observation carried forward; LS Mean = least-squares mean; SE= standard error.
[a] Subjects with a baseline value and at least 1 postbaseline value at or prior to the respective visits are included.
[b] LS mean (SE) and p-value based on an analysis of covariance model for the change from baseline at the respective visits, with treatment group, baseline disease-modifying antirheumatic drug (DMARD) use, and study as factors, and the baseline value as a covariate. P-values in italics for the pooled analysis are ≤ 0.050 and considered nominally significant as there was no adjustment for multiplicity.
Note: For subjects who discontinued from the study prior to Week 16, the last available postbaseline value observed prior to discontinuation was carried forward to Weeks 16 and 24. For subjects who entered early escape (EE) at Week 16 or who did not enter EE but discontinued from the study between Weeks 16 and 24, the last available postbaseline value observed prior to EE or discontinuation, respectively, was carried forward to Week 24. Missing values for subjects who did not discontinue or enter EE were imputed using the last available postbaseline value prior to the visit in question.
Source: Table 2.5.1, Table 2.5.2, Table 2.15.3.

At Week 52, the mean change from baseline in the HAQ-DI score ranged from -0.192 to -0.369 in the APR 20 BID treatment group and from -0.318 to -0.350 in the APR 30 BID treatment group.

MCID for HAQ-DI for PSA has not been fully evaluated. The improvements in the HAQ-DI score observed in the APR 20 BID and APR 30 BID treatment groups exceeded the estimated MCID of -0.13 provided by the Kwok, 2010 study but not the estimated –MCID of -0.3 and -0.35 provided in two Mease studies [Mease, 2004a and Mease 2011] .

Other Secondary Efficacy Endpoints

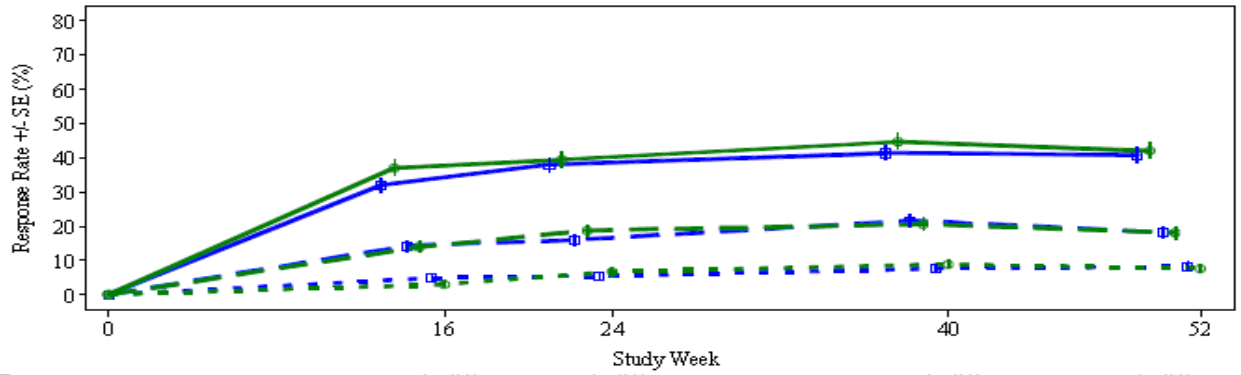
Modified ACR 50/70 endpoint

In all three pivotal Phase 3 studies, numerically greater proportions of subjects treated with apremilast achieved a modified ACR 50 at both time points compared with placebo. The treatment effect at Week 16 in modified ACR 50 was nominally significant for the APR 20 BID treatment group in Studies PSA-002

(26/168 (15.5) p= 0.0049) and PSA-003 (24/163 (14.7) p= 0.0034) and for the APR 30 BID treatment group in Study PSA-002 (27/168 (16.1) p= 0.0027). This is maintained at Week 24 in both apremilast treatment groups, and nominally significant for the APR 20 BID group in Study PSA-002, and APR 30 BID group in Studies PSA-002 and PSA-004 (Table 23 and 25).

The proportions of subjects achieving modified ACR 70 responses at Week 16 were nominally significant in the APR 20 BID treatment group (10/168 (6.0%) p= 0.0192) at Week 16 and the APR 20 BID (9/168 (5.4%) p= 0.0104) and APR30 BID (17/168 (10.1%) p= 0.0001) groups at week 24 in Stud PSA-002 only.

Table 30 - Modified ACR 20/50/70 Responses During Weeks 0-52 in Subjects Initially Randomized to Apremilast (Pooled Analysis;
NRI)



Treatment	n/m (%)	n/m (%)	n/m (%)	n/m (%)
ACR 20 - 20 mg BID	160/500 (32.0)	190/500 (38.0)	207/500 (41.4)	204/500 (40.8)
ACR 20 - 30 mg BID	184/497 (37.0)	196/497 (39.4)	222/497 (44.7)	209/497 (42.1)
ACR 50 - 20 mg BID	71/500 (14.2)	80/500 (16.0)	108/500 (21.6)	91/500 (18.2)
ACR 50 - 30 mg BID	69/497 (13.9)	93/497 (18.7)	102/497 (20.5)	90/497 (18.1)
ACR 70 - 20 mg BID	24/500 (4.8)	27/500 (5.4)	38/500 (7.6)	41/500 (8.2)
ACR 70 - 30 mg BID	15/497 (3.0)	33/497 (6.6)	44/497 (8.9)	38/497 (7.6)

Pain

Subject's Assessment of Pain Score

Statistically significantly greater improvements in the subject's assessment of pain score, compared with placebo, were observed at Week 16 in the APR 30 BID treatment group in Studies PSA-002 and PSA-004. These improvements were generally maintained at Week 24. A dose effect was observed in two of the three studies (PSA-002 and PSA-004). The MCID of a 10-mm improvement (reduction) from baseline (Dworkin, 2008) was exceeded at Week 16 in the APR 20 BID treatment group in Studies PSA-002 and PSA-003, and in the APR 30 BID treatment group in all three studies and were generally maintained at Week 24.

Non articular symptoms Enthesitis, Dactylitis and Psoriasis

The ACR criteria and other composite responder indices (e.g. PsARC and the EULAR response criteria) have discriminated between placebo and treatment response. However, they do not incorporate skin, and entheseal involvement. Response rates were evaluated in patients with pre-existing enthesitis and Dactylitis at baseline. In the pooled analysis the mean reduction in MASES from baseline in the APR 30 BID treatment group was nominally significantly greater compared with the placebo group at week 24. (-1.4 p= 0.0194).

In subjects with pre-existing dactylitis, in the pooled analysis nominally significantly greater mean reductions (indicating improvement) in dactylitis severity score were observed in the APR30 BID treatment group, compared with placebo, at Weeks 16 (-1.7 p= 0.049) and 24 (-1.8 p= 0.0097).

In the pivotal Phase 3 studies, PASI-75 response rates at week 16 were nominally significant compared with placebo for the APR20 BID and APR30 BID groups in all three studies with the response for the 30 mg BID group in PSA-004 achieving statistical significance at week 16. Response rates were 4.5% to 5.7% for PBO and 18.8% to 20.9% for APR20BID and 22.1-22.2% for APR30 BID groups respectively. These response rates were maintained through week 24 and from week 24-52. At Week 52, the PASI-75 response rates were 24.5% to 28.6% in the APR 20 BID treatment group and 36.8% to 39.3% in the APR 30 BID treatment group. Similar responses were seen for PASI-50. A dose effect in favour of APR30 BID for the PASI-50 and PASI-75 response was observed at Week 52 in all three studies.

SF-36v2 Physical Functioning Domain Score

Statistically significant improvements (increases), compared with placebo, in the SF-36v2 physical functioning domain score at Week 16 in the APR 30 BID treatment group in all three pivotal Phase 3 studies and in the APR 20 BID treatment group in Study PSA-002.

FACIT-fatigue Score

At baseline, the mean FACIT-F scores were 29.9. Mean change from baseline were nominally statistically significant across the APR 30 BID groups in all studies PSA 002,003 and 004 at weeks 16 and 24 although values recorded at week 24 across all three studies were slightly lower than those recorded at week 16 suggesting a slight diminution of effect.

BASDAI Assessments

Axial involvement, a common secondary feature of peripheral predominant PsA disease, was present in 37% (548/1493) of subjects enrolled in the Phase 3 program. This subgroup had a mean (median) baseline BASDAI score of 5.95 (6.17). In the pooled analysis, a nominally significantly greater reduction (improvement) in the BASDAI score was observed in the APR 30 BID treatment group, compared with placebo, at Weeks 16 (-0.57 p=0.0173)and 24 (-0.853 p=0.0002). The number of patients with predominantly spondylitic subtypes of psoriatic arthritis(2.1% of study poopulation) was too small to allow meaningful assessment.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 31 - Summary of efficacy for three pivotal trials for psoriatic arthritis indication

	A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety studies of two doses of apremilast in subjects with active psoriatic arthritis		
Study identifier		Pivotal trials PSA-002 PSA- 003, PSA-004	
Design		These phase 3 parallel-group study with 2 active treatment groups consisted of 2 treatment phases: a 24- week, randomized, double-blind, placebo-controlled phase, and a 236-week active treatment/long-term safety phase consisting of 2 parts (a randomized, double-blind active treatment phase of at least 28 weeks 'duration, and an open-label, long-term safety phase of up to 4 years' duration), for an overall study Duration of 5 years.	
	Duration of main phase: Duration of Extension phase:		24 weeks The 24 week placebo controlled phase was followed by an active treatment period in which all subjects were to be treated up to 5 years in total. 52 week data presented as part of this application for all three studies.
Treatments groups Study PSA002	Apremilast30mBID		N=168
	Apremilast 20mgBID		N=168
	Placebo		N=168
Treatment groups Study PSA003	Apremilast30mBID		N=162
	Apremilast 20mgBID		N=163
	Placebo		N=159
Treatment groups Study PSA004	Apremilast30mBID		N=167
	Apremilast 20mgBID		N=169
	Placebo		N=169

Endpoints and definitions	**Primary endpoint**	The primary endpoint was the proportion of subjects in each apremilast treatment group(APR 20 BID and APR 30 BID), compared with placebo, who achieved a modified ACR 20 response after 16 weeks of therapy
	Key secondary endpoint	Change from baseline in physical function (HAQ-DI) after 16 weeks of treatment.
	Other secondary endpoints	**Physical Function endpoints:** SF-36v2 Physical Functioning domain score **Quality of Life endpoints**: SF-36v2 PCS and MCS (FACIT-Fatigue) score **Other indices of disease activity:** (DAS28[CRP]) (CDAI) EULAR response BASDAI **Non-articular manifestations of psoriatic disease** (MASES) Dactylitis Severity Score
	Results and Analysis	
Analysis description		**Primary Analysis**

Analysis population and time point description		Two analysis periods were defined for the analysis of efficacy: The placebo-controlled period (Weeks 0-24) The apremilast-exposure period (Weeks 0-52) Efficacy analyses were conducted using 3 analysis populations: The Full Analysis Set (FAS) - the primary population for the analyses of efficacy during the placebo-controlled period. The Per-Protocol (PP) Population - used for supportive analyses of efficacy during the placebo-controlled period. The Apremilast Subjects as Initially Randomized/Re-randomized (AAR) - used for the analyses of efficacy during the apremilast-exposure period		
Proportion of Subjects Achieving a Modified ACR 20Response at Week 16 in Studies PSA-002, PSA-003, and PSA-004 (FAS; NRI)	**PSA002**	**Placebo**	**APR20mg BID**	**APR30mg BID**
	Number of subject	n/N (%)	n/N (%)	n/N (%)
	Modified ACR 20 (FAS NRI) Week 16 **Treatment effect**	32/168 (19.0)	51/168 (30.4) **11.3**	64/168 (38.1) **19.0**
	p-value **(diff v PLB**		0.0166	0.001
	PSA003	**Placebo**	**APR20mg BID**	**APR30mg BID**
	Number of subject	n/N (%)	n/N (%)	n/N (%)
	Modified ACR 20 Response at Week 16 **Treatment effect**	30/159 (18.9)	61/163 (37.4) 18.7	52/162 (32.1) 13.4
	p-value **(diff v PLB**		0.0002	0.0060

	PSA004	**Placebo**	**APR20mg BID**	**APR30mg BID**
	Number of subject	n/N (%)	n/N (%)	n/N (%)
	Modified ACR 20 Response at Week 16 **Treatment effect (p-value) (diff v PLB)**	31/169 (18.3)	48/169 (28.4) 9.8 (0.0295)	68/167 (40.7) 22.3 (< 0.0001)
	Pooled analysis	Placebo	APR20mg BID	APR30mg BID
	Number of subject	n/N (%)	n/N (%)	n/N (%)
	Modified ACR 20 Response at Week 16 **Treatment effect (p-value) (diff v PLB)**	93/496 (18.8)	160/500 (32.0) 13.2 (< 0.0001)	68/497 (37.0) 18.3 (< 0.0001)
Change from Baseline in HAQ-DI at Week 16 in Studies PSA-002, PSA-003, and PSA-004 (FAS; LOCF)				
	PSA002	Placebo	APR20mg BID	APR30mg BID

		Mean Baseline Value 1.206 LS Mean Change (SE) 0.086 (0.0360)	Mean Baseline Value 1.141 LS Mean Change (SE) -0.198 (0.0364) LS Mean Diff. v. PLB -0.113 P value= 0.0252	Mean Baseline Value 1.231 LS Mean Change (SE) -0.244 (0.0364) LS Mean Diff v PLB -0.159 P value= 0.0017
	PSA-003	Placebo	APR20mg BID	APR30mg BID
		Mean Baseline Value 1.147 LS Mean Change (SE) -0.053 (0.0358)	Mean Baseline Value 1.141 LS Mean Change (SE) -0.157 (0.0351) LS Mean Diff v PLB -0.104 P value=0.0320	Mean Baseline Value 1.231 LS Mean Change (SE) -0.193 (0.0354) LS Mean Diff v PLB -0.140 P value= 0.0042
	PSA-004	Placebo	APR20mg BID	APR30mg BID
		Mean Baseline Value 1.160 LS Mean Change (SE) -0.065 (0.0335)	Mean Baseline Value 1.134 LS Mean Change (SE) -0.131 (0.0337) LS Mean Diff v PLB -0.066 P value -0.1619	Mean Baseline Value 1.160 LS Mean Change (SE) -0.192 (0.0339) LS Mean Diff v PLB -0.127 P value= 0.0073
Notes		Additional analyses of the primary and secondary endpoints at week 24 and 52 and modified ACR 50 and to a lesser extent ACR70 responses and, PsARC, were supportive of the modified ACR 20 and HAQ-DI findings where there were sufficient numbers of subjects for meaningful conclusions. SF-36v2 physical functioning domain score, MASES, dactylitis severity score, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), were evaluated.		
Analysis description		**Secondary analysis**		

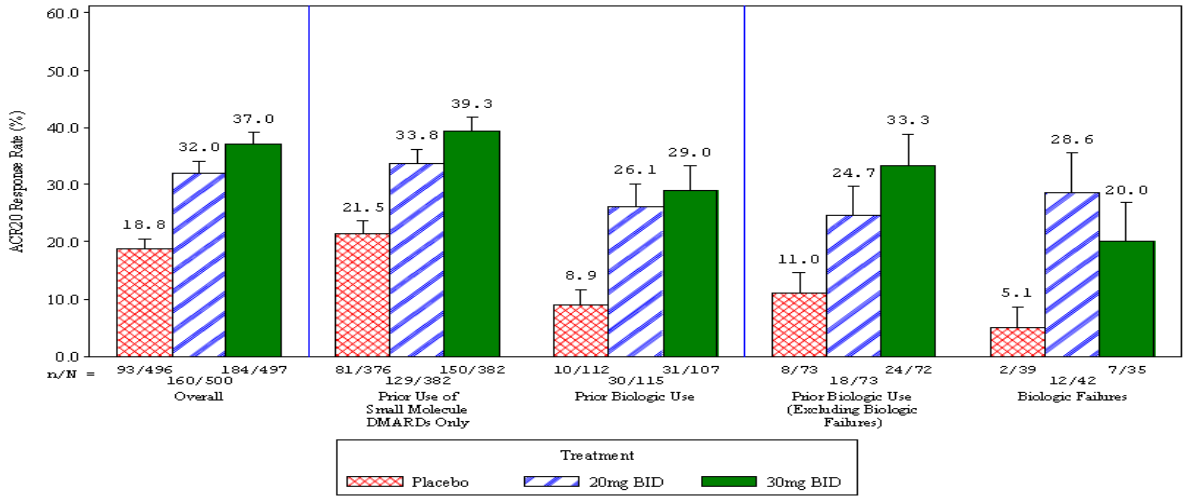
Effect estimate per comparison	**Primary endpoint** **ACR20(FAS:NRI)**	Comparison groups at 16 weeks	APR20mg BID vs. PBO	APR30mg vs. PLB
	PSA002	Difference in %	11.3%	19%
		P-value	0.0166	0.0001
	PSA003	Difference in %	18.7%	13.4%
		P-value	0.0002	0.0060
	PSA004	Difference in %	9.8%	22.3%
		P-value	0.0295	< 0.0001
	Secondary endpoint	Comparison groups	APR20mg BID vs. PBO	APR30mg vs. PLB
	HAQ-DI	Adjusted difference of mean	-0.113	-0.159
	PSA-002	P-value	0.0252	0.0017
	PSA-003	Adjusted difference of mean	-0.104	-0.140
		P-value	0.0320	0.0042
	PSA-004	Adjusted difference of mean	-0.066	-0.127
		P-value	0.1619	0.0073

Analysis performed across trials (pooled analyses and meta-analysis)

Prior DMARD use

Both the APR 20 BID and APR 30 BID treatment groups had greater modified ACR 20 responses at Week 16 versus placebo, irrespective of the number or type of prior small-molecule or biologic DMARDs used, including subjects who had had a therapeutic failure to biologics. These treatment effects were generally maintained at Week 24.

Figure 3 - Modified ACR 20 Response at Week 16 by Prior Biologic DMARD Use (Pooled Analysis; FAS; NRI)

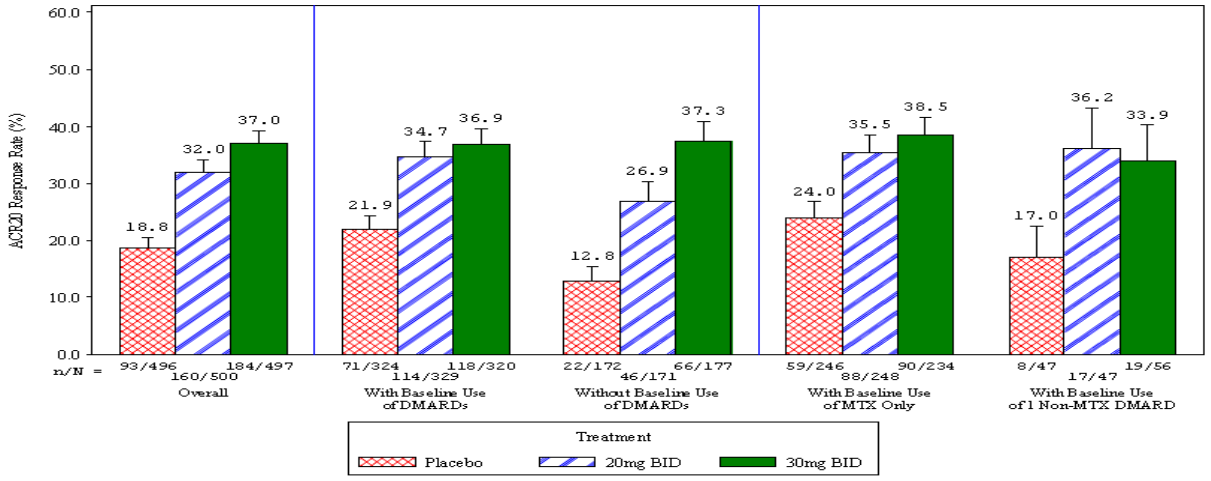


ACR 20 = 20% improvement per American College of Rheumatology response criteria; BID = twice daily; DMARD = disease-modifying antirheumatic drug; FAS = full analysis set; NRI = non-responder imputation.
Note: Error bars denote standard error.
Note: Subjects who discontinued early prior to Week 16 and subjects who did not have sufficient data for a definitive determination of response status at Week 16 are counted as non-responders.
Source: Table 2.1.1 and Table 3.1.1.

Baseline (Concomitant) DMARD Use

Higher modified ACR 20 responses were observed in the APR 20 BID and APR 30 BID treatment groups compared with placebo at Week 16, irrespective of whether apremilast was given alone or in combination with small-molecule DMARDs. Treatment effect ended to be higher in the non-MTX subgroup compared with the MTX treated subgroup even though the change from baseline was lower than that seen in the MTX treated group.

Figure 4 - Modified ACR 20 Response at Week 16 by Baseline Small-Molecule DMARD Use (Pooled Analysis; FAS; NRI)



ACR 20 = 20% improvement per American College of Rheumatology response criteria; BID = twice daily; DMARD = disease-modifying antirheumatic drug; FAS = full analysis set; MTX = methotrexate; NRI = non-responder imputation.
Note: Error bars denote standard error.
Note: Subjects who discontinued early prior to Week 16 and subjects who did not have sufficient data for a definitive determination of response status at Week 16 are counted as non-responders.
Source: Table 2.1.1 and Table 3.1.1.

Supportive Study

Study PSA-005 is an ongoing phase 3 parallel group study in 528 subjects with active PsA. It differs from the pivotal three Phase 3 studies in that subjects enrolled in Study PSA-005 have not been previously

treated with a DMARD, and concomitant DMARDs, including MTX, LEF, and SSZ, were prohibited. It has a similar design to the pivotal phase studies. A statistically significantly greater proportion of subjects in the APR 20 BID and APR 30 BID treatment groups achieved a modified ACR 20 response at Week 16 (the primary endpoint) compared with placebo (28.0% and 30.7%, respectively, versus 15.9%; p = 0.0062 and 0.0010, respectively). Statistically significant modified ACR 20 responses at Week 24 for APR 20 BID and APR 30BID treated subjects. (29.1% and 24.4%, respectively, versus placebo at 13.1%; p = 0.0002 and p = 0.0063, respectively).

The results of Study PSA-005 are broadly in line with the results of the three pivotal studies.

PLAQUE PSORIASIS

The pivotal Phase 3 studies of apremilast for monotherapy use in psoriasis (Studies PSOR-008 and PSOR-009) utilized a similar study design and are described below.

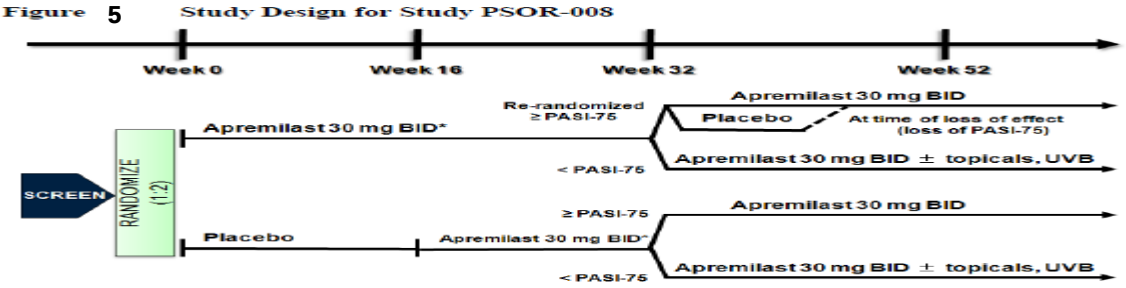
Study PSOR-008 (ESTEEM 1): A phase 3, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.

Study PSOR-009 (ESTEEM 2)*:* A phase 3, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.

Methods

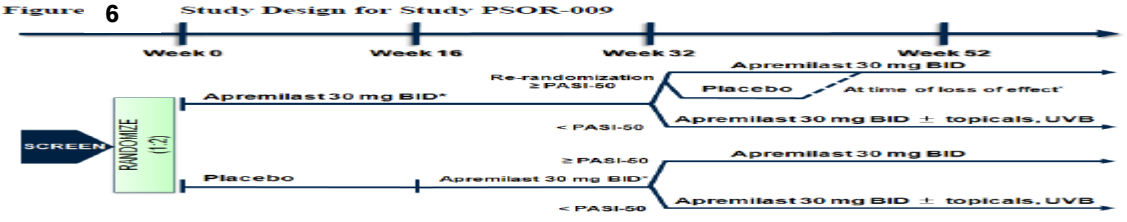
A total of 1257 subjects were enrolled across both studies. These studies consist of 4 treatment phases (see Figure 5 and 6): a 16-week, randomized, double-blind, placebo-controlled phase; a 16-week double-blind maintenance phase; a 20-week randomized, double-blind treatment withdrawal phase; and a 208-week, open-label long-term safety extension phase. Overall study duration is 5 years. The application contains data from the initial 52 weeks of dosing, spanning the first 3 treatment phases. The long-term extension phases across both studies are ongoing.

Figure 5 Study Design for Study PSOR-008



BID = twice daily; PASI = Psoriasis Area and Severity Index; UVB = ultraviolet B light.
Note: Placebo-controlled Phase = Weeks 0 to 16, Maintenance Phase = Weeks 16 to 32, Randomized Treatment Withdrawal Phase = Weeks 32 to 52. * Doses of apremilast were titrated over the first 6 days of administration. During the Randomized Treatment Withdrawal Phase, subjects were switched to apremilast at the time of loss of PASI-75 (< PASI 75), but no later than Week 52. A responder was defined as a subject achieving ≥ PASI-75, a partial responder was defined as a subject achieving PASI-50 to PASI-74, and a nonresponder was defined as a subject achieving < PASI-50.

Figure 6 Study Design for Study PSOR-009



BID = twice daily; PASI = Psoriasis Area and Severity Index; UVB = ultraviolet B light.
Note: Placebo-controlled Phase = Weeks 0 to 16, Maintenance Phase = Weeks 16 to 32, Randomized Treatment Withdrawal Phase = Weeks 32 to 52. * Doses of apremilast were titrated over the first 6 days of administration. During the Randomized Treatment Withdrawal Phase, subjects were switched to apremilast at time of loss of effect, defined as time of loss of 50% of the PASI improvement obtained at Week 32 compared to baseline, but no later than Week 52.

Study Participants

Subjects enrolled in these studies needed to have a diagnosis of moderate to severe plaque psoriasis with the following eligibility criteria at baseline:

- ≥ 10% body surface area (BSA) involvement
- PASI score ≥ 12
- sPGA score ≥ 3 (moderate or greater) at baseline, and being candidates for
- candidates for systemic and/or phototherapy.

The study population included subjects who were either treatment naïve or who had received phototherapy and/or systemic therapy and who were considered appropriate candidates for systemic therapy based on the European S3-Guidelines. The use of concomitant psoriasis therapies, other than a limited spectrum of topical agents, was not allowed during the Placebo-controlled and the Maintenance Phases. Only low potency corticosteroids for the face, axillae, and groin; coal-tar shampoo and salicylic acid preparations for the scalp; and unmedicated skin moisturiser for body lesions were permitted. These topical therapies were not to be used within 24 hours prior to a study visit.

Treatments

Eligible subjects were randomised to receive APR 30 mg twice daily (APR 30 BID) or identically-appearing placebo during the 16-week Placebo-controlled Phase. In accordance with the titration schedule, subjects in the APR 30 mg BID treatment group reached the target dose on the sixth day of treatment. At Week 16, all subjects originally assigned to placebo were transitioned in a blinded fashion to receive APR 30 mg BID and dose-titrated during their first 6 days of active treatment, while subjects originally assigned to APR 30 BID continued to receive APR 30 BID in a blinded fashion up to Week 32 (Maintenance Phase).

In Study PSOR-008 at Week 32 (Randomised Treatment Withdrawal Phase), subjects originally randomised to APR 30 mg BID at baseline who had achieved a PASI-75 response were re-randomised to either APR 30 mg BID or placebo to evaluate time to first loss of PASI-75 response. Subjects who were re-randomised to placebo and lost their PASI-75 response restarted APR 30 mg BID without re-titration.

In Study PSOR-009 a different definition of responder, a loss of effect in the Randomised Treatment Withdrawal phase was utilised. Consequently, at Week 32 (Randomised Treatment Withdrawal Phase), subjects originally randomised to APR 30 mg BID at baseline who had achieved a PASI-50 response at Week 32, were re-randomised to either APR 30 mg BID or placebo to evaluate the time to first loss of 50% of the Week 32 PASI improvement compared to baseline. Subjects who were re-randomised to placebo and lost 50% of their Week 32 PASI response restarted APR 30 mg BID without re-titration.

Subjects who had been randomised to APR 30 mg BID at baseline and who did not achieve a PASI-75 response in Study PSOR-008 or a PASI-50 response in Study PSOR-009 were not re-randomised in the Randomised Treatment Withdrawal Phase. In addition, all subjects who had been randomised to placebo at baseline were not re-randomised in the Randomised Treatment Withdrawal Phase regardless of their PASI response. Subjects who were not re-randomised continued to receive APR 30 mg BID up to Week 52. Subjects who did not achieve a PASI-75 response in Study PSOR-008 or a PASI-50 response in Study PSOR-009 at Week 32 were given the option of adding topical and/or UVB phototherapy to APR 30 mg BID treatment at the investigator's discretion at Week 32 only, but therapy could be initiated at any time during Weeks 32 to 52.

Objectives

<u>Primary:</u>

The primary objective of the pivotal studies was to evaluate the clinical efficacy of APR 30 mg BID compared with placebo, in subjects with moderate to severe plaque PSOR.

Secondary:

The secondary objectives of the pivotal studies were to:

- Evaluate the safety and tolerability of apremilast 30 mg BID, compared with placebo, in subjects with moderate to severe plaque PSOR

- Evaluate the effect of apremilast 30 mg BID, compared with placebo, on quality of life in subjects with moderate to severe plaque PSOR

Outcomes/endpoints

The primary endpoint of both studies was the proportion of subjects treated with either APR 30 mg BID or placebo who achieved a PASI-75 response at Week 16 compared to baseline.

The major secondary endpoint was the proportion of subjects treated with either APR 30mg BID or placebo with an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16 (Feldman, 2005).

Other endpoints: Body Surface Area; Pruritus Visual Analog Scale Assessment; Dermatology Life Quality Index; Patient Health Questionnaire Depression Scale; Nail Psoriasis Severity Index; Scalp Physician Global Assessment; Palmoplantar Psoriasis Physician Global Assessment; Medical Outcome Study Short Form 36-item Health Survey; European Quality of Life-5 Dimensions Questionnaire; Work Limitations Questionnaire-25.

Sample size

Approximately 825 subjects were to be randomised into PSOR-008, with 550 subjects in APR 30 mg BID arm and 275 subjects in the placebo arm and 405 subjects were to be randomised into PSOR-009, with 270 subjects on APR 30 mg BID and 135 on placebo. Sample size estimation for the primary endpoint was based on results of the Phase 2b study, PSOR-005. A chi-square test with a 0.05 2-sided significance level provided 90% power to detect a 20% difference (30% versus 10%) between APR 30 mg BID and placebo for the proportion of subjects achieving at least a PASI-75 at Week 16 when the total sample size was approximately 189 with a 2:1 randomisation.

Randomisation

Subjects were randomised in a 2:1 ratio to receive either apremilast 30 mg BID or placebo, using the IVRS. After 16 weeks of treatment, all subjects originally randomised to placebo were switched to receive apremilast 30 mg BID. In order to evaluate the time to relapse/loss of effect, at Week 32, subjects who were initially randomised to apremilast 30 mg BID and had achieved a response, were re-randomised to either placebo or apremilast 30 mg BID in a 1:1 ratio. No stratification factor was utilized in these studies.

Blinding (masking)

Blinding was maintained by the use of identical blister cards for all subjects.

Statistical methods

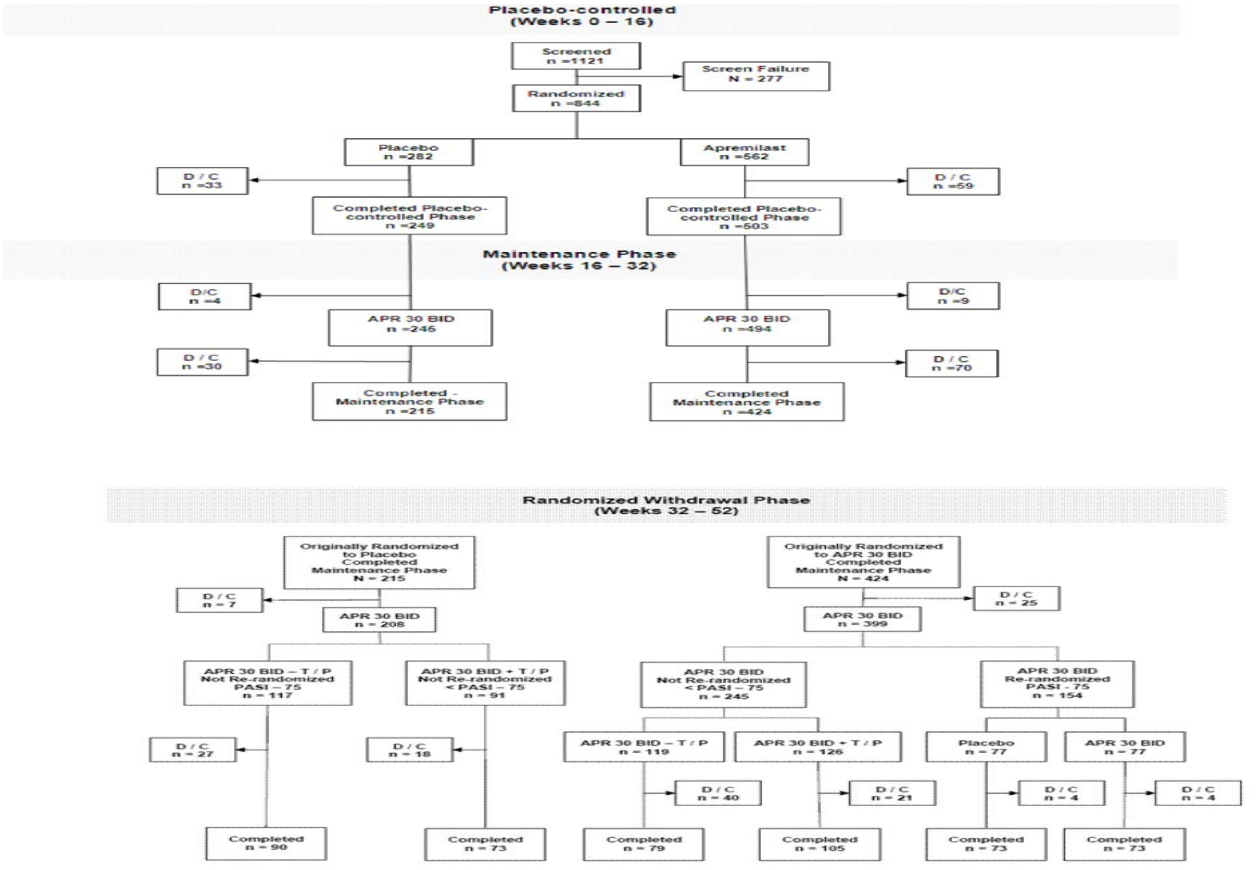
The statistical methods and missing data handling approaches were identical in the two individual studies. The analysis of the primary efficacy endpoint, PASI-75 response at Week 16 was compared between APR 30 mg BID and placebo using LOCF and a two-sided Chi-Square test. Supportive analyses were performed for: (1) FAS population treating missing values as nonresponders (NRI), (2) FAS population treating

dropouts due to adverse event or lack of efficacy as non-responders and other dropouts using LOCF, (3) PP population using LOCF method for imputing missing values, (4) Analyses using CMH test stratified by pooled sites for FAS population using LOCF method for imputing missing values. The major secondary endpoint, sPGA response, was analyzed similarly, conditioned on observing a statistically significant result for the primary endpoint.

Results

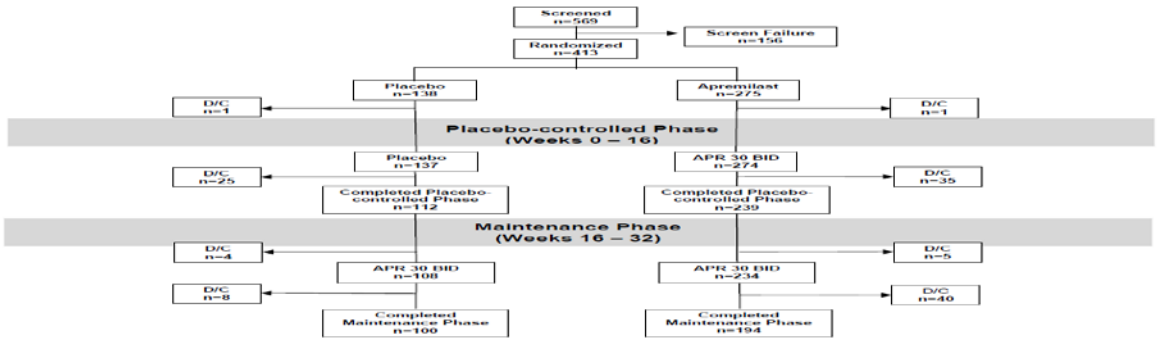
Participant flow

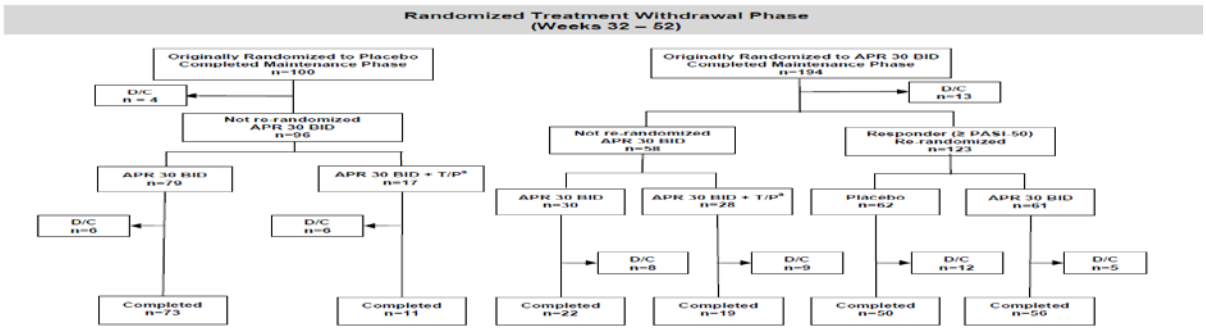
Figure 7 - Subject Disposition in Study PSOR-008



APR 30 BID = apremilast 30 mg twice daily; D/C = discontinued; PASI = Psoriasis Area and Severity Index; T/P = topical or phototherapy.
Source: Report CC-10004-PSOR-008, Table 14.1.1, Table 14.1.2.1, Table 14.1.2.2, Table 14.1.2.3.1, Table 14.1.2.3.2.

Figure 8 - Subject Disposition in Study PSOR-009





APR 30 BID = apremilast 30 mg twice daily; D/C = discontinued; T/P = topical or phototherapy.
a Nonresponders could have T/P added to their APR 30 BID regimen at the investigator's discretion.
Source: Report CC-10004-PSOR-009, Table 14.1.1, Table 14.1.2.1, Table 14.1.2.2, Table 14.1.2.3.1, Table 14.1.2.3.2.

Recruitment

PSOR-008:

Study initiation date: 22 September 2010

Study completion date: 02 November 2011 (Week 52)

PSOR-009:

Study initiation date: 30 November 2010

Study completion date: 24 November 2011 (Week 52)

Conduct of the study

In study PSOR-008 the changes to the protocol included 4 protocol amendments.

In study PSOR-009 the changes to the protocol included 3 protocol amendments.

Baseline data

The demographic characteristics of subjects at baseline were similar across studies, were generally well balanced across treatment groups, and were representative of a typical population in psoriasis clinical trials (Table 32). In Study PSOR-008 and Study PSOR-009, the majority of subjects were white (89.7% and 92.0%, respectively) and male (67.9% and 67.2%, respectively) with a median age of 46.0 years. Generally, mean weight and mean BMI were comparable across Study PSOR-008 (93.38 kg and 31.26 kg/m2, respectively) and Study PSOR-009 (91.10 kg and 30.80 kg/m2, respectively). Additionally, in both studies, approximately one-half of subjects were obese (≥ 30 kg/m2) and one-fourth of subjects were morbidly obese (≥ 35 kg/m2).

In general, the patient demographic profile of Studies PSOR-008 and PSOR-009 was considered comparable to patients with moderate to severe psoriasis. Approximately one third of subjects in Study PSOR-008 were from US sites and about one-third from Canadian sites; approximately 14% each were from sites in Europe and the Rest of World. In Study PSOR-009, approximately 50%, 22%, and 28% of subjects were from sites in the US, Canada, and Europe, respectively.

Table 32: Baseline Demographic Characteristics in Studies PSOR-008 and PSOR-009 (FAS)

Demographic Characteristic	PSOR-008			PSOR-009		
	Placebo (n = 282)	APR 30 BID (n = 562)	Total (N = 844)	Placebo (n = 137)	APR 30 BID (n = 274)	Total (N = 411)
Age, years						
n	282	562	844	137	274	411
Mean ± SD	46.5 ± 12.72	45.8 ± 13.07	46.0 ± 12.95	45.7 ± 13.38	45.3 ± 13.05	45.4 ± 13.15
Median (min – max)	46.0 (20 – 82)	46.0 (18 – 80)	46.0 (18 – 82)	46.0 (22 – 73)	45.5 (18 – 83)	46.0 (18 – 83)
Age category 1, n (%)						
< 65 years	258 (91.5)	514 (91.5)	772 (91.5)	123 (89.8)	252 (92.0)	375 (91.2)
≥ 65 years	24 (8.5)	48 (8.5)	72 (8.5)	14 (10.2)	22 (8.0)	36 (8.8)
Age category 2, n (%)						
< 40 years	91 (32.3)	183 (32.6)	274 (32.5)	49 (35.8)	98 (35.8)	147 (35.8)
40 to < 65 years	167 (59.2)	331 (58.9)	498 (59.0)	74 (54.0)	154 (56.2)	228 (55.5)
65 to < 75 years	19 (6.7)	45 (8.0)	64 (7.6)	14 (10.2)	21 (7.7)	35 (8.5)
75 to < 85 years	5 (1.8)	3 (0.5)	8 (0.9)	0	1 (0.4)	1 (0.2)
≥ 85 years	0	0	0	0	0	0
Sex, n (%)						
Male	194 (68.8)	379 (67.4)	573 (67.9)	100 (73.0)	176 (64.2)	276 (67.2)
Female	88 (31.2)	183 (32.6)	271 (32.1)	37 (27.0)	98 (35.8)	135 (32.8)

Demographic Characteristic	PSOR-008			PSOR-009		
	Placebo (n = 282)	APR 30 BID (n = 562)	Total (N = 844)	Placebo (n = 137)	APR 30 BID (n = 274)	Total (N = 411)
Race, n (%)						
American Indian or Alaska Native	5 (1.8)	2 (0.4)	7 (0.8)	1 (0.7)	1 (0.4)	2 (0.5)
Asian	16 (5.7)	28 (5.0)	44 (5.2)	6 (4.4)	8 (2.9)	14 (3.4)
Black or African American	10 (3.5)	18 (3.2)	28 (3.3)	2 (1.5)	13 (4.7)	15 (3.6)
Native Hawaiian or Other Pacific Islander	1 (0.4)	5 (0.9)	6 (0.7)	0	1 (0.4)	1 (0.2)
White	250 (88.7)	507 (90.2)	757 (89.7)	128 (93.4)	250 (91.2)	378 (92.0)
Other	0	2 (0.4)	2 (0.2)	0	1 (0.4)	1 (0.2)
Ethnicity, n (%)						
Hispanic or Latino	13 (4.6)	32 (5.7)	45 (5.3)	20 (14.6)	37 (13.5)	57 (13.9)
Not Hispanic or Latino	269 (95.4)	530 (94.3)	799 (94.7)	117 (85.4)	237 (86.5)	354 (86.1)
Region, n (%)						
USA	98 (34.8)	196 (34.9)	294 (34.8)	65 (47.4)	141 (51.5)	206 (50.1)
Canada	106 (37.6)	211 (37.5)	317 (37.6)	30 (21.9)	62 (22.6)	92 (22.4)
Europe	37 (13.1)	80 (14.2)	117 (13.9)	42 (30.7)	71 (25.9)	113 (27.5)
Rest of the World	41 (14.5)	75 (13.3)	116 (13.7)	0	0	0
Weight, kg						
n	282	562	844	137	274	411
Mean ± SD	93.69 ± 23.227	93.22 ± 21.376	93.38 ± 21.999	90.51 ± 22.474	91.40 ± 23.026	91.10 ± 22.820
Median (min – max)	92.00 (45.0 – 185.9)	90.20 (46.0 – 175.1)	90.90 (45.0 – 185.9)	85.20 (51.0 – 191.1)	90.45 (46.5 – 196.0)	88.90 (46.5 – 196.0)

Demographic Characteristic	PSOR-008			PSOR-009		
	Placebo (n = 282)	APR 30 BID (n = 562)	Total (N = 844)	Placebo (n = 137)	APR 30 BID (n = 274)	Total (N = 411)
Alcoholic beverage drinking, n (%)						
Yes	196 (69.5)	390 (69.4)	586 (69.4)	82 (59.9)	176 (64.2)	258 (62.8)
No	86 (30.5)	172 (30.6)	258 (30.6)	55 (40.1)	98 (35.8)	153 (37.2)
Tobacco use, n (%)[b]						
Current user	92 (32.6)	202 (35.9)	294 (34.8)	61 (44.5)	101 (36.9)	162 (39.4)
Past user	77 (27.3)	158 (28.1)	235 (27.8)	29 (21.2)	63 (23.0)	92 (22.4)
Non-user	112 (39.7)	201 (35.8)	313 (37.1)	47 (34.3)	110 (40.1)	157 (38.2)
Missing	1 (0.4)	1 (0.2)	2 (0.2)	0	0	0

APR = apremilast; BMI = body mass index; FAS = full analysis set; min – max = minimum to maximum; SD = standard deviation; USA = United States of America.
[a] Body mass index was based on the last weight measurement taken prior to the first dose of investigational product and the height measurement taken at screening.
[b] The past user category excludes subjects who were also current users.
Source: PSOR-008 CSR Table 12, PSOR-009 CSR Table 12.

Table 33: Baseline Demographic Characteristics (Pooled Analysis; FAS)

Demographic Characteristic	Placebo (n = 419)	APR 30 BID (n = 836)	Total (N = 1255)
Age, years			
n	419	836	1255
Mean ± SD	46.2 ± 12.93	45.6 ± 13.06	45.8 ± 13.01
Median (min – max)	46.0 (20 – 82)	46.0 (18 – 83)	46.0 (18 – 83)
Age category 1, n (%)			
< 65 years	381 (90.9)	766 (91.6)	1147 (91.4)
≥ 65 years	38 (9.1)	70 (8.4)	108 (8.6)
Age category 2, n (%)			
< 40 years	140 (33.4)	281 (33.6)	421 (33.5)
40 to < 65 years	241 (57.5)	485 (58.0)	726 (57.8)
65 to < 75 years	33 (7.9)	66 (7.9)	99 (7.9)
75 to < 85 years	5 (1.2)	4 (0.5)	9 (0.7)
≥ 85 years	0 (0.0)	0 (0.0)	0 (0.0)
Sex, n (%)			
Male	294 (70.2)	555 (66.4)	849 (67.6)
Female	125 (29.8)	281 (33.6)	406 (32.4)
Race, n (%)			
American Indian or Alaska Native	6 (1.4)	3 (0.4)	9 (0.7)
Asian	22 (5.3)	36 (4.3)	58 (4.6)
Black or African American	12 (2.9)	31 (3.7)	43 (3.4)
Native Hawaiian or Other Pacific Islander	1 (0.2)	6 (0.7)	7 (0.6)
White	378 (90.2)	757 (90.6)	1135 (90.4)
Other	0 (0.0)	3 (0.4)	3 (0.2)

Baseline Disease History and Characteristics

The disease history and disease activity of subjects was generally well balanced across studies and between treatment groups (Table 34). In Study PSOR-008, the median duration of plaque psoriasis was 16.95 years (mean of 19.40 years). Almost all of the subjects (95.9%) had a history of scalp psoriasis and the majority of subjects had a history of nail psoriasis (68.5%). The median BSA affected was 20.00% (mean of 24.71%) and the median PASI score at baseline was 16.80 (mean of 18.95). The majority of subjects (70.3%) had a sPGA score of 3 (moderate), and more than 99% had 3 (moderate) or 4 (severe) sPGA at baseline.

In Study PSOR-009, the median duration of plaque psoriasis (time elapsed since diagnosis) was 15.80 years (mean of 18.19 years). Almost all of the subjects (92.7%) had a history of scalp psoriasis and the majority of subjects had a history of nail psoriasis (67.6%). The median BSA affected was 21.50% (mean of 26.17%) and the median PASI score at baseline was 16.80 (mean of 19.30). The majority of subjects (69.6%) had an sPGA score of 3 (moderate), and more than 99% had 3 (moderate) or 4 (severe) sPGA at baseline.

Approximately 30% of subjects in both studies had severe disease, as measured by an sPGA of 4 (severe) or a PASI > 20. In addition, approximately 50% or more of the subjects in each study had a BSA involvement of > 20%, another measure of severe disease.

Table 34: Psoriasis Disease History and Baseline Values (Pooled Analysis; FAS)

Disease Characteristic	PSOR-008			PSOR-009		
	Placebo (n = 282)	APR 30 BID (n = 562)	Total (N = 844)	Placebo (n = 137)	APR 30 BID (n = 274)	Total (N = 411)
Duration of plaque psoriasis (years since diagnosis)						
n	280	562	842	135	271	406
Mean ± SD	18.68 ±12.355	19.75 ± 13.041	19.40 ± 12.820	18.68 ± 12.088	17.94 ± 11.367	18.19 ± 11.602
Median (min – max)	16.10 (1.2 – 50.9)	17.45 (1.1 – 70.7)	16.95 (1.1 – 70.7)	17.20 (0.9 – 51.8)	15.40 (1.1 – 51.9)	15.80 (0.9 – 51.9)
History of:						
Guttate, pustular, or erythrodermic psoriasis	12 (4.3)	26 (4.6)	38 (4.5)	15 (10.9)	25 (9.1)	40 (9.7)
Scalp psoriasis	273 (96.8)	536 (95.4)	809 (95.9)	128 (93.4)	253 (92.3)	381 (92.7)
Nail psoriasis	200 (70.9)	378 (67.3)	578 (68.5)	96 (70.1)	182 (66.4)	278 (67.6)
Palmoplantar psoriasis	83 (29.4)	154 (27.4)	237 (28.1)	44 (32.1)	71 (25.9)	115 (28.0)
Psoriatic arthritis	50 (17.7)	123 (21.9)	173 (20.5)	13 (9.5)	42 (15.3)	55 (13.4)
Baseline values						
Total PASI score						
n	282	562	844	137	274	411
Mean ± SD	19.37 ± 7.392	18.74 ± 7.182	18.95 ± 7.254	20.04 ± 7.995	18.93 ± 7.058	19.30 ± 7.392
Median (min – max)	17.55 (12.0 – 59.3)	16.60 (12.0 – 60.0)	16.80 (12.0 – 60.0)	17.80 (11.2 – 53.3)	16.55 (12.0 – 57.8)	16.80 (11.2 – 57.8)
PASI Score Category, n (%)						
≤ 20	195 (69.1)	404 (71.9)	599 (71.0)	88 (64.2)	193 (70.4)	281 (68.4)
>20	87 (30.9)	158 (28.1)	245 (29.0)	49 (35.8)	81 (29.6)	130 (31.6)

Disease Characteristic	PSOR-008			PSOR-009		
	Placebo (n = 282)	APR 30 BID (n = 562)	Total (N = 844)	Placebo (n = 137)	APR 30 BID (n = 274)	Total (N = 411)
BSA affected (%)						
n	282	562	844	137	274	411
Mean ± SD	25.34 ± 14.647	24.40 ± 14.716	24.71 ± 14.691	27.58 ± 15.822	25.46 ± 15.416	26.17 ± 15.565
Median (min – max)	21.30 (10.0 – 84.0)	20.00 (9.0 – 86.0)	20.00 (9.0 – 86.0)	23.50 (10.0 – 78.0)	21.00 (10.0 – 86.0)	21.50 (10.0 – 86.0)
BSA category, n (%)						
≤ 20	133 (47.2)	296 (52.7)	429 (50.8)	57 (41.6)	131 (47.8)	188 (45.7)
>20	149 (52.8)	266 (47.3)	415 (49.2)	80 (58.4)	143 (52.2)	223 (54.3)
sPGA, n (%)						
0 (clear)	0	0	0	0	0	0
1 (almost clear)	0	0	0	0	0	0
2 (mild)	1 (0.4)	0	1 (0.1)	0	1 (0.4)	1 (0.2)
3 (moderate)	192 (68.1)	401 (71.4)	593 (70.3)	88 (64.2)	198 (72.3)	286 (69.6)
4 (severe)	89 (31.6)	161 (28.6)	250 (29.6)	49 (35.8)	75 (27.4)	124 (30.2)
PPPGA, n (%)						
0 (clear)	195 (69.1)	391 (69.6)	586 (69.4)	89 (65.0)	195 (71.2)	284 (69.1)
1 (minimal)	22 (7.8)	49 (8.7)	71 (8.4)	14 (10.2)	23 (8.4)	37 (9.0)
2 (mild)	37 (13.1)	63 (11.2)	100 (11.8)	16 (11.7)	29 (10.6)	45 (10.9)
3 (moderate)	23 (8.2)	45 (8.0)	68 (8.1)	13 (9.5)	20 (7.3)	33 (8.0)
4 (severe)	3 (1.1)	12 (2.1)	15 (1.8)	3 (2.2)	6 (2.2)	9 (2.2)
Missing	2 (0.7)	2 (0.4)	4 (0.5)	2 (1.5)	1 (0.4)	3 (0.7)

Disease Characteristic	PSOR-008			PSOR-009		
	Placebo (n = 282)	APR 30 BID (n = 562)	Total (N = 844)	Placebo (n = 137)	APR 30 BID (n = 274)	Total (N = 411)
ScPGA, n (%)						
0 (clear)	13 (4.6)	32 (5.7)	45 (5.3)	9 (6.6)	23 (8.4)	32 (7.8)
1 (minimal)	19 (6.7)	37 (6.6)	56 (6.6)	13 (9.5)	26 (9.5)	39 (9.5)
2 (mild)	58 (20.6)	117 (20.8)	175 (20.7)	20 (14.6)	48 (17.5)	68 (16.5)
3 (moderate)	117 (41.5)	255 (45.4)	372 (44.1)	60 (43.8)	119 (43.4)	179 (43.6)
4 (severe)	62 (22.0)	104 (18.5)	166 (19.7)	28 (20.4)	48 (17.5)	76 (18.5)
5 (very severe)	10 (3.5)	15 (2.7)	25 (3.0)	5 (3.6)	9 (3.3)	14 (3.4)
Missing	3 (1.1)	2 (0.4)	5 (0.6)	2 (1.5)	1 (0.4)	3 (0.7)
Total NAPSI, score for target nail						
n	195	366	561	91	175	266
Mean ± SD	4.3 ± 2.16	4.2 ± 2.03	4.3 ± 2.07	4.4 ± 2.05	4.2 ± 2.13	4.2 ± 2.10
Median (min – max)	4.0 (1 – 8)	4.0 (0 – 8)	4.0 (0 – 8)	4.0 (1 – 8)	4.0 (1 – 8)	4.0 (1 – 8)

Prior Use of Psoriasis-related Therapies

The psoriasis-related therapies that were previously used by subjects prior to enrolment in the study were similar across the 2 studies and were generally well balanced across treatment groups (Table 35). In both studies, approximately 55% of the subjects had been treated previously with systemic therapy (i.e., conventional systemic and/or biologics). Approximately 40% of subjects were previously treated with conventional systemic therapies (including treatment failures), approximately 30% had prior exposure to biologics (including treatment failures), and 17% to 29% had prior exposure to TNF blockers. Approximately one-third of subjects had received prior phototherapy. Approximately one-third of the

subjects (35.2% in Study PSOR-008 and 35.8% in Study PSOR-009) were naive to prior systemic and/or phototherapy.

Table 35: Prior Psoriasis Therapies

	Number (%) of Subjects					
	PSOR-008			PSOR-009		
	Placebo (n = 282)	APR 30 BID (n = 562)	Total (N = 844)	Placebo (n = 137)	APR 30 BID (n = 274)	Total (N = 411)
Prior systemic and/or phototherapies						
0	101 (35.8)	196 (34.9)	297 (35.2)	55 (40.1)	92 (33.6)	147 (35.8)
1	82 (29.1)	159 (28.3)	241 (28.6)	34 (24.8)	78 (28.5)	112 (27.3)
2	46 (16.3)	114 (20.3)	160 (19.3)	21 (15.3)	50 (18.2)	71 (17.3)
≥ 3	53 (18.8)	93 (16.5)	146 (17.3)	27 (19.7)	54 (19.7)	81 (19.7)
Failed prior systemic and/or phototherapies[a]						
0	111 (39.4)	238 (42.3)	349 (41.4)	48 (35.0)	105 (38.3)	153 (37.2)
1	51 (18.1)	81 (14.4)	132 (15.6)	21 (15.3)	52 (19.0)	73 (17.8)
2	13 (4.6)	26 (4.6)	39 (4.6)	8 (5.8)	14 (5.1)	22 (5.4)
≥ 3	6 (2.1)	21 (3.7)	27 (3.2)	5 (3.6)	11 (4.0)	16 (3.9)
Prior systemic therapies[b]						
0	132 (46.8)	261 (46.4)	393 (46.6)	64 (46.7)	117 (42.7)	181 (44.0)
1	74 (26.2)	156 (27.8)	230 (27.3)	34 (24.8)	79 (28.8)	113 (27.5)
2	43 (15.2)	81 (14.4)	124 (14.7)	19 (13.9)	45 (16.4)	64 (15.6)
≥ 3	33 (11.7)	64 (11.4)	97 (11.5)	20 (14.6)	33 (12.0)	53 (12.9)
Failed prior systemic therapies[a]						
0	99 (35.1)	221 (39.3)	320 (37.9)	49 (35.8)	103 (37.6)	152 (37.0)
1	36 (12.8)	47 (8.4)	83 (9.8)	12 (8.8)	36 (13.1)	48 (11.7)
2	11 (3.9)	17 (3.0)	28 (3.3)	7 (5.1)	10 (3.6)	17 (4.1)
≥3	4 (1.4)	16 (2.8)	20 (2.4)	5 (3.6)	8 (2.9)	13 (3.2)
Prior phototherapies[c]						
0	194 (68.8)	386 (68.7)	580 (68.7)	106 (77.4)	191 (69.7)	297 (72.3)
1	79 (28.0)	161 (28.6)	240 (28.4)	28 (20.4)	75 (27.4)	103 (25.1)
2	9 (3.2)	15 (2.7)	24 (2.8)	3 (2.2)	7 (2.6)	10 (2.4)
≥ 3	0	0	0	0	1 (0.4)	1 (0.2)
Failed prior phototherapies[a]						
0	62 (22.0)	107 (19.0)	169 (20.0)	19 (13.9)	49 (17.9)	68 (16.5)
1	24 (8.5)	63 (11.2)	87 (10.3)	12 (8.8)	31 (11.3)	43 (10.5)
2	2 (0.7)	6 (1.1)	8 (0.9)	0	3 (1.1)	3 (0.7)
≥ 3	0	0	0	0	0	0

	Number (%) of Subjects					
	PSOR-008			PSOR-009		
	Placebo (n = 282)	APR 30 BID (n = 562)	Total (N = 844)	Placebo (n = 137)	APR 30 BID (n = 274)	Total (N = 411)
Prior conventional systemic therapies[d]						
0	180 (63.8)	350 (62.3)	530 (62.8)	84 (61.3)	168 (61.3)	252 (61.3)
1	67 (23.8)	148 (26.3)	215 (25.5)	34 (24.8)	75 (27.4)	109 (26.5)
2	24 (8.5)	47 (8.4)	71 (8.4)	12 (8.8)	23 (8.4)	35 (8.5)
≥ 3	11 (3.9)	17 (3.0)	28 (3.3)	7 (5.1)	8 (2.9)	15 (3.6)
Failed prior conventional systemic therapies[a]						
0	66 (23.4)	152 (27.0)	218 (25.8)	35 (25.5)	68 (24.8)	103 (25.1)
1	30 (10.6)	45 (8.0)	75 (8.9)	10 (7.3)	32 (11.7)	42 (10.2)
2	4 (1.4)	10 (1.8)	14 (1.7)	7 (5.1)	6 (2.2)	13 (3.2)
≥3	2 (0.7)	5 (0.9)	7 (0.8)	1 (0.7)	0	1 (0.2)
Prior biologic therapies						
0	202 (71.6)	400 (71.2)	602 (71.3)	93 (67.9)	182 (66.4)	275 (66.9)
1	46 (16.3)	112 (19.9)	158 (18.7)	31 (22.6)	57 (20.8)	88 (21.4)
2	26 (9.2)	33 (5.9)	59 (7.0)	10 (7.3)	19 (6.9)	29 (7.1)
≥ 3	8 (2.8)	17 (3.0)	25 (3.0)	3 (2.2)	16 (5.8)	19 (4.6)
Failed prior biologic therapies[a]						
0	61 (21.6)	125 (22.2)	186 (22.0)	33 (24.1)	68 (24.8)	101 (24.6)
1	13 (4.6)	25 (4.4)	38 (4.5)	7 (5.1)	13 (4.7)	20 (4.9)
2	6 (2.1)	6 (1.1)	12 (1.4)	2 (1.5)	5 (1.8)	7 (1.7)
≥3	0	6 (1.1)	6 (0.7)	2 (1.5)	6 (2.2)	8 (1.9)
Prior TNF blocker therapies						
0	234 (83.0)	461 (82.0)	695 (82.3)	107 (78.1)	202 (73.7)	309 (75.2)
1	38 (13.5)	83 (14.8)	121 (14.3)	24 (17.5)	49 (17.9)	73 (17.8)
2	8 (2.8)	12 (2.1)	20 (2.4)	4 (2.9)	16 (5.8)	20 (4.9)
≥ 3	2 (0.7)	6 (1.1)	8 (0.9)	2 (1.5)	7 (2.6)	9 (2.2)

Numbers analysed

PSOR-008

Table 36: Number of Subjects Included in Data Sets Analyzed in the Placebo-controlled Phase (Weeks 0 to 16; Randomized Subjects)

	Placebo N=282 n (%)	APR 30 BID N = 562 n (%)	Total N = 844 n (%)
Full Analysis Set[a]	282 (100.0)	562 (100.0)	844 (100.0)
Per protocol Population[b]	276 (97.9)	555 (98.8)	831 (98.5)
Safety Population[c]	282 (100.0)	560 (99.6)	842 (99.8)

APR 30 BID = apremilast 30 mg twice daily; IP = investigational product; PASI = Psoriasis Area and Severity Index' sPGA = static Physician Global Assessment; [a] Subjects who were randomized as specified in the protocol. Subjects who were randomized in error and did not have IP dispensed were excluded from full analysis set; [b] Subjects who were randomized according to the protocol, received at least 1 dose of IP, had at least 1 postbaseline PASI or sPGA evaluation, and had no protocol violations that may substantially affect the results of the primary and major secondary endpoint evaluation; [c] Subjects who were randomized and received at least 1 dose of IP.

PSOR-009

Table 37: Number of Subjects Included in Data Sets Analyzed in the Placebo-controlled Phase (Weeks 0 to 16; Randomized Subjects)

Data Set	Placebo N=138 n (%)	APR 30 BID N=275 n (%)	Total N=413 n (%)
Full analysis set[a]	137 (99.3)	274 (99.6)	411 (99.5)
Per protocol population[b]	134 (97.1)	266 (96.7)	400 (96.9)
Safety population[c]	136 (98.6)	272 (98.9)	408 (98.8)

APR 30 BID = apremilast 30 mg twice daily; IP = investigational product; PASI = Psoriasis Activity and Severity Index; sPGA = static Physician Global Assessment; a Subjects who were randomized as specified in the protocol. Subjects who were randomized in error and did not have IP dispensed were excluded from full analysis set; b Subjects who were randomized according to the protocol, received at least one dose of IP, had at least 1 postbaseline PASI or sPGA evaluation, and had no protocol violations that may have substantially affect the results of the primary and major secondary endpoint evaluation; c Subjects who were randomized and received at least one dose of IP.

Outcomes and estimation

Comparison of Results of Individual Studies

The individual study results from Studies PSOR-008 and PSOR-009 are presented side-by-side in this section to demonstrate the consistency of effect observed with apremilast in the treatment of subjects with moderate to severe plaque psoriasis

Placebo-controlled Phase (Weeks 0 to 16)

Primary Efficacy Analysis

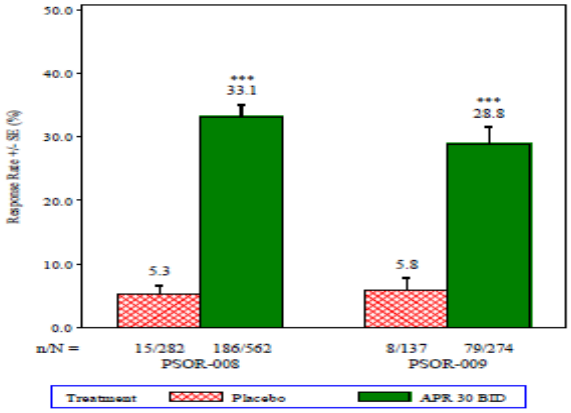
The primary efficacy endpoint in both studies was the proportion of subjects achieving at least a 75% reduction from baseline in the PASI score (PASI-75) at Week 16 (Table 38 and Figure 9).

Table 38 - Proportion of Subjects Achieving a PASI-75 at Week 16 in Studies PSOR-008 and PSOR-009 (FAS; LOCF).

Endpoint	PSOR-008		PSOR-009	
	Placebo (n = 282)	APR 30 BID (n = 562)	Placebo (n = 137)	APR 30 BID (n = 274)
Subjects achieving PASI-75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
Treatment comparison (apremilast – placebo)				
Difference in proportions (95% CI)[a]	--	27.8 (23.1, 32.5)	--	23.0 (16.3, 29.6)
2-sided p-value[b]	--	**< 0.0001**	--	**< 0.0001**

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index.
[a] Two-sided 95% CI is based on the normal approximation.
[b] Two-sided p-value is based on the two-sided chi-square test. P-values in bold are considered statistically significant.
Source: PSOR-008 CSR Table 25, PSOR-009 CSR Table 25.

Figure 9 - Proportion of Subjects Achieving a PASI-75 at Week 16 in Studies PSOR-008 and PSOR-009 (FAS; LOCF)



APR = apremilast; BID = twice daily; FAS = full analysis set; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index; SE = standard error.
Note: *** p < 0.0001; all comparisons relative to placebo.
Source: PSOR-008 CSR Figure 3, PSOR-009 CSR Figure 3.

In both studies, a statistically significantly greater proportion of subjects in the APR 30 BID treatment group achieved the primary endpoint, compared with placebo ($p < 0.0001$ for both studies), as evaluated using the primary analysis method (ie, missing values at Week 16 imputed using LOCF). The response rates for the placebo and APR 30 BID treatment groups were 5.3% and 33.1%, respectively, in Study PSOR-008 and were 5.8% and 28.8%, respectively, in Study PSOR-009. In both studies, the placebo response rates were low, as typically observed in well-conducted psoriasis trials.

Sensitivity Analyses for the Primary Endpoint

The results for the primary endpoint were supported by the sensitivity analyses conducted to assess the impact of missing data in the:

1. FAS population treating subjects with missing values as nonresponders (nonresponder imputation [NRI])
2. FAS population treating dropouts due to an AE or lack of efficacy as nonresponders and other dropouts using LOCF
3. PP population using the LOCF method for imputing missing values
4. FAS population using the LOCF method for imputing values stratified by geographical region, and
5. FAS population using the LOCF method for imputing values stratified by pooled sites.

All these sensitivity analyses demonstrated similar results and statistically significant differences between the APR 30 mg BID treatment group compared with the placebo treatment group (p <0.0001 for all sensitivity analyses). Additionally, the potential for site treatment interaction was analyzed by pooling sites within each region to create “sites” that had a prespecified minimum of 30 subjects (site pooling is discussed in the individual study statistical analysis plans. This analysis demonstrated statistically significant treatment differences in both studies for the APR 30 mg BID treatment group compared with the placebo treatment group, results that were similar to the analysis using a chi-square test (Table 39).

Table 39: Sensitivity Analyses for Primary Endpoint (PASI-75 Response at Week 16) for Studies PSOR-008 and PSOR-009

Study	Analysis Population	Imputation	Placebo n/N (%)	APR 30 BID		
				n/N (%)	Treatment Comparison (Apremilast - Placebo)	
					P-value	Difference in Proportions (95% CI)
PSOR-008	FAS	NRI[a]	11/282 (3.9)	118/562 (21.0)	< 0.0001[b]	17.1 (13.0, 21.2)
	FAS[c]	NRI/LOCF	11/282 (3.9)	122/562 (21.7)	< 0.0001[b]	17.8 (13.7, 21.9)
	PP[d]	LOCF	11/276 (4.0)	121/555 (21.8)	< 0.0001[b]	17.8 (13.7, 22.0)
	FAS	LOCF[e]	11/282 (3.9)	122/562 (21.7)	< 0.0001[e]	17.9 (13.9, 22.0)
	FAS	LOCF[f]	11/282 (3.9)	122/562 (21.7)	< 0.0001[f]	18.5 (14.5, 22.5)
PSOR-009	FAS	NRI[a]	5/137 (3.6)	54/274 (19.7)	< 0.0001[b]	16.1 (10.4, 21.7)
	FAS[c]	NRI/LOCF	5/137 (3.6)	56/274 (20.4)	< 0.0001[b]	16.8 (11.1, 22.5)
	PP[d]	LOCF	6/134 (4.5)	56/266 (21.1)	< 0.0001[b]	16.6 (10.6, 22.6)
	FAS	LOCF[e]	6/137 (4.4)	56/274 (20.4)	< 0.0001[e]	16.1 (10.3, 21.9)
	FAS	LOCF[f]	6/137 (4.4)	56/274 (20.4)	< 0.0001[f]	16.7 (10.8, 22.6)

APR = apremilast; BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; FAS = full analysis set; LOCF = last observation carried forward; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PP = Per Protocol; sPGA = static Physician Global Assessment; USA = United States of America.

[a] Nonresponder imputation counted subjects as nonresponders if they discontinued prior to Week 16 or who had missing sPGA evaluations.

[b] Two-sided p-value is based on the two-sided chi-square test. Two-sided 95% CI is based on the normal approximation.

[c] FAS population treating dropouts due to adverse event or lack of efficacy as nonresponders and other dropouts using LOCF.

[d] The PP included all subjects who were randomized according to the protocol, received at least one dose of IP, had at least one postbaseline PASI and sPGA evaluation, and had no protocol violations that may have substantially affected the results of the primary and major secondary endpoint evaluation.

[e] Analyses stratified by geographical region. Sites in the same region/country were pooled into strata as USA, Canada, Europe, and the Rest of the World. Adjusted difference in proportions is the weighted average of the treatment differences across the above strata using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average. Two-sided p-value is based on the CMH test adjusting for the above strata.

[f] The pooling strategy was to ensure that each pooled site had 30 or more subjects. Pooling was conducted within 4 regions: USA, Canada, Europe, and the Rest of the World. Sites from a country with more than 30 subjects were not pooled with sites from other countries. The adjusted difference in proportions is the weighted average of the treatment differences across the strata using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average. Two-sided p-value is based on the CMH test adjusting for the above strata.

Source: PSOR-008 CSR Table 28, PSOR-009 CSR Table 28.

Major Secondary Efficacy Analysis

The major secondary endpoint in both studies was the proportion of subjects achieving sPGA score of 0 (clear) or 1 (almost clear), with at least a 2-point reduction from baseline at Week 16.

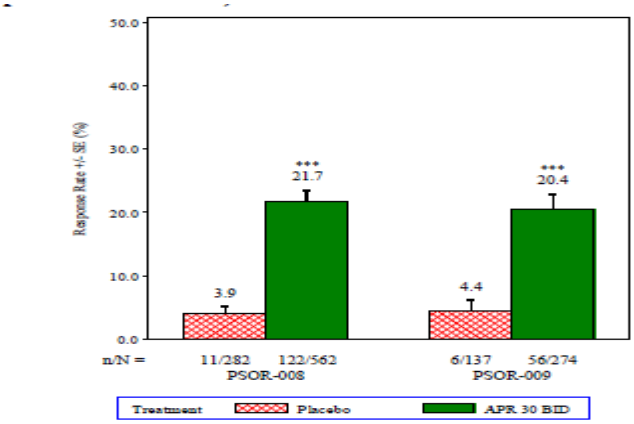
In both studies, a statistically significantly greater proportion of subjects in the APR 30 BID treatment group achieved the endpoint compared with placebo (p < 0.0001) (Table 40 and Figure 10). The response rates in the placebo and APR 30 BID treatment groups were 3.9% and 21.7%, respectively, in Study PSOR-008, and were 4.4% and 20.4%, respectively, in Study PSOR-009.

Table 40: Proportion of Subjects Who Achieved a Secondary Response (sPGA Response at Week 16) in Studies PSOR-008 and PSOR-009 (FAS; LOCF)

Endpoint	PSOR-008		PSOR-009	
	Placebo (n = 282)	APR 30 BID (n = 562)	Placebo (n = 137)	APR 30 BID (n = 274)
Subjects achieving sPGA of 0 or 1 with at least a 2-point reduction from baseline, n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)
Treatment comparison (apremilast – placebo)				
Difference in proportions (95% CI)[a]	--	17.8 (13.7, 21.9)	--	16.1 (10.2, 21.9)
2-sided p-value[a]	--	**< 0.0001**	--	**< 0.0001**

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; sPGA = static Physician Global Assessment.
[a] Two-sided 95% CI is based on the normal approximation. Two-sided p-value is based on the two-sided chi-square test. P-values in bold are considered statistically significant.
Note: sPGA response is defined as sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
Source: PSOR-008 CSR Table 27, PSOR-009 CSR Table 27.

Figure 10 - Proportion of Subjects Who Achieved a Secondary Response (sPGA Response at Week 16) in Studies PSOR-008 and PSOR-009 (FAS; LOCF)



APR = apremilast; BID = twice daily; FAS = full analysis set; LOCF = last observation carried forward; sPGA = static Physician Global Assessment.
Note: *** p < 0.0001; all comparisons relative to placebo. sPGA response is defined as sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
Source: PSOR-008 CSR Table 14.2.2.1.1.1, PSOR-009 CSR Table 14.2.2.1.1.1.

Sensitivity Analyses for the Major Secondary Endpoint

The results for the major secondary endpoint were supported by the same sensitivity analyses conducted for the primay endpoint.

These sensitivity analyses demonstrated similar results and statistically significant differences for the APR 30 mg BID treatment group compared with the placebo treatment group (p <0.0001 for all sensitivity analyses).

Additionally, the potential for site treatment interaction was analyzed by pooling sites within each region to create “sites” that had a prespecified minimum of 30 subjects. The 2-sided p-value was >0.05 in both studies, indicating no statistically significant interaction. Among sensitivity analyses, the CMH test adjusted by pooled site was performed for sPGA. This analysis demonstrated statistically significant treatment differences in both studies for the APR 30 mg BID treatment group compared with the placebo treatment group, results that were similar to the analysis using achi-square test (Table 41).

Table 41: Sensitivity Analyses for the Major Secondary Endpoint (sPGA Response at Week 16) for Studies PSOR-008 and PSOR-009.

Study	Analysis Population	Imputation	Placebo n/N (%)	APR 30 BID		
				n/N (%)	Treatment Comparison (Apremilast - Placebo)	
					P-value	Difference in Proportions (95% CI)
PSOR-008	FAS	NRI[a]	11/282 (3.9)	118/562 (21.0)	< 0.0001[b]	17.1 (13.0, 21.2)
	FAS[c]	NRI/LOCF	11/282 (3.9)	122/562 (21.7)	< 0.0001[b]	17.8 (13.7, 21.9)
	PP[d]	LOCF	11/276 (4.0)	121/555 (21.8)	< 0.0001[b]	17.8 (13.7, 22.0)
	FAS	LOCF[e]	11/282 (3.9)	122/562 (21.7)	< 0.0001[e]	17.9 (13.9, 22.0)
	FAS	LOCF[f]	11/282 (3.9)	122/562 (21.7)	< 0.0001[f]	18.5 (14.5, 22.5)
PSOR-009	FAS	NRI[a]	5/137 (3.6)	54/274 (19.7)	< 0.0001[b]	16.1 (10.4, 21.7)
	FAS[c]	NRI/LOCF	5/137 (3.6)	56/274 (20.4)	< 0.0001[b]	16.8 (11.1, 22.5)
	PP[d]	LOCF	6/134 (4.5)	56/266 (21.1)	< 0.0001[b]	16.6 (10.6, 22.6)
	FAS	LOCF[e]	6/137 (4.4)	56/274 (20.4)	< 0.0001[e]	16.1 (10.3, 21.9)
	FAS	LOCF[f]	6/137 (4.4)	56/274 (20.4)	< 0.0001[f]	16.7 (10.8, 22.6)

APR = apremilast; BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; FAS = full analysis set; LOCF = last observation carried forward; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PP = Per Protocol; sPGA = static Physician Global Assessment; USA = United States of America.

[a] Nonresponder imputation counted subjects as nonresponders if they discontinued prior to Week 16 or who had missing sPGA evaluations.

[b] Two-sided p-value is based on the two-sided chi-square test. Two-sided 95% CI is based on the normal approximation.

[c] FAS population treating dropouts due to adverse event or lack of efficacy as nonresponders and other dropouts using LOCF.

[d] The PP included all subjects who were randomized according to the protocol, received at least one dose of IP, had at least one postbaseline PASI and sPGA evaluation, and had no protocol violations that may have substantially affected the results of the primary and major secondary endpoint evaluation.

[e] Analyses stratified by geographical region. Sites in the same region/country were pooled into strata as USA, Canada, Europe, and the Rest of the World. Adjusted difference in proportions is the weighted average of the treatment differences across the above strata using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average. Two-sided p-value is based on the CMH test adjusting for the above strata.

[f] The pooling strategy was to ensure that each pooled site had 30 or more subjects. Pooling was conducted within 4 regions: USA, Canada, Europe, and the Rest of the World. Sites from a country with more than 30 subjects were not pooled with sites from other countries. The adjusted difference in proportions is the weighted average of the treatment differences across the strata using CMH weights. Two-sided 95% CI is based on a normal approximation to the weighted average. Two-sided p-value is based on the CMH test adjusting for the above strata.

Source: PSOR-008 CSR Table 28, PSOR-009 CSR Table 28.

Endpoints in Studies PSOR-008 and PSOR-009 were analyzed in a hierarchical fashion to control the Type I error rate, as outlined in the studies' statistical analysis plans (Section 10.2 of the PSOR-008 SAP serves as a representative example).

Composite Endpoint: PASI-75 and sPGA Response at Week 16

The composite endpoint was defined as the number of subjects who achieved both a PASI-75 and sPGA scores of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16.

In both pivotal studies, a nominally significantly greater proportion of subjects in the APR 30 BID treatment group achieved the composite endpoint at Week 16 compared with placebo (nominal $p < 0.0001$) (Table 42). Similar findings were observed in the PP population.

Table 42: Proportion of Subjects Achieving Both PASI-75 and sPGA Score Response at Week 16 (Composite Endpoint) in Studies PSOR-008 and PSOR-009 (FAS; LOCF)

Endpoint	PSOR-008		PSOR-009	
	Placebo (n = 282)	APR 30 BID (n = 562)	Placebo (n = 137)	APR 30 BID (n = 274)
Subjects achieving both PASI-75 and sPGA response, n (%)	10 (3.5)	114 (20.3)	6 (4.4)	51 (18.6)
Treatment comparison (apremilast – placebo)				
Difference in proportions (95% CI)[a]	--	16.7 (12.8, 20.7)	--	14.2 (8.5, 20.0)
2-sided p-value[a]	--	*< 0.0001*	--	*< 0.0001*

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index; sPGA = static Physician Global Assessment.

[a] Two-sided 95% CI is based on the normal approximation. Two-sided p-value is based on the two-sided chi-square test. P-values in italics are ≤ 0.050 and considered nominally significant based on hierarchical testing.

Note: sPGA response is defined as an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.

Source: PSOR-008 CSR Table 36, PSOR-009 CSR Table 36.

Percent Change in Body Surface Area Involvement From Baseline at Week 16

Affected BSA is a measure of the percentage of BSA that is covered by psoriasis lesions, with >20% being a measure of "severe" disease (Winterfield, 2004). The mean affected BSA involvement in both studies was approximately 25% at baseline. Approximately half of the subjects had a baseline BSA >20%.

In both pivotal studies, subjects treated with APR 30 mg BID achieved statistically significant improvement (reduction) in the change from baseline in psoriasis affected BSA at Week 16 compared with placebo (p <0.0001) (Table 43). The mean percent changes from baseline in BSA involvement for the placebo and APR 30 mg BID treatment groups were -6.94% and -47.80%, respectively, in Study PSOR-008 and were -6.14% and -48.45%, respectively, in Study PSOR-009.

Table 43: Percent Change From Baseline in Psoriasis Affected BSA at Week 16 in Studies PSOR-008 and PSOR-009 (FAS; LOCF)

	PSOR-008		PSOR-009	
Visit	Placebo (n = 282)	APR 30 BID (n = 562)	Placebo (n = 137)	APR 30 BID (n = 274)
Baseline, n[a]	278	559	136	269
Mean ± SD	25.03 ± 14.272	24.37 ± 14.687	27.64 ± 15.863	25.53 ± 15.540
Median (min – max)	21.05 (10.0 – 84.0)	20.00 (10.0 – 86.0)	23.75 (10.0 – 78.0)	21.00 (10.0 – 86.0)
Week 16				
Mean ± SD	23.18 ± 16.314	13.16 ± 13.979	26.15 ± 19.293	13.33 ± 14.251
Median (min – max)	18.00 (0.8 – 83.0)	9.00 (0 – 87.0)	21.00 (0.0 – 86.0)	8.50 (0.0 – 83.0)
Mean % change from Baseline ± SD	-6.94 ± 38.947	-47.80 ± 38.480	-6.14 ± 47.567	-48.45 ± 40.781
Median % change from Baseline (min – max)	-5.48 (-93.8 – 213.0)	-52.50 (-100.0 – 205.6)	-8.02 (-100.0 – 230.8)	-54.55 (-100.0 – 130.0)
LS mean (95% CI)[b]	-6.99 (-11.54, -2.44)	-47.77 (-50.98, -44.56)	-6.25 (-13.54, 1.05)	-48.40 (-53.58, -43.22)
Treatment comparison (apremilast – placebo)				
Difference in LS means (2-sided 95% CI)[b]	--	-40.78 (-46.34, -35.21)	--	-42.15 (-51.11, -33.20)
2-sided p-value[b]	--	**< 0.0001**	--	**< 0.0001**

APR = apremilast; BID = twice daily; BSA = body surface area; CI = confidence interval; FAS = full analysis set; LOCF = Last observation carried forward; LS = least squares; min – max = minimum to maximum; SD = standard deviation.

[a] Subjects with a baseline value and at least 1 postbaseline value are included.

[b] Based on an analysis of covariance model for the percent change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate. P-values in bold are considered statistically significant.

Note: Negative change indicates improvement.

Source: PSOR-008 CSR Table 30, PSOR-009 CSR Table 30.

Percent Change in PASI Score From Baseline at Week 16

In both pivotal studies, subjects treated with APR 30 mg BID achieved a statistically significant improvement (reduction) in PASI score from baseline at Week 16 compared with placebo (p <0.0001). The mean percent changes in PASI score for the placebo and APR 30 mg BID treatment groups were -16.7% and -52.1%, respectively, in Study PSOR-008, and were -15.8% and -50.9%, respectively, in Study PSOR-009 (Table 44). The median percent changes in PASI score for the placebo and APR 30 mg BID treatment groups were -14.0% and -59.0%, respectively, in Study PSOR-008, and were -18.0% and -56.0%, respectively, in Study PSOR-009.

Table 44: Percent Change in PASI Score From Baseline at Week 16

Visit	PSOR-008		PSOR-009	
	Placebo (n = 282)	APR 30 BID (n = 562)	Placebo (n = 137)	APR 30 BID (n = 274)
Baseline, n[a]	278	559	136	269
Mean ± SD	19.32 ± 7.357	18.73 ± 7.167	20.09 ± 7.998	18.99 ± 7.102
Median (min – max)	17.45 (12.0 – 59.3)	16.60 (12.0 – 60.0)	17.85 (11.2 – 53.3)	16.60 (12.0 – 57.8)
Week 16				
Mean ± SD	16.23 ± 9.043	9.08 ± 7.784	17.15 ± 11.011	9.42 ± 7.683
Median (min – max)	14.70 (1.2 – 53.9)	7.2 (0.0 – 60.0)	14.85 (0.0 – 56.7)	7.20 (0.0 – 44.4)
Mean percent change from baseline ± SD	-16.7 ± 31.52	-52.1 ± 32.81	-15.8 ± 41.33	-50.9 ± 34.00
Median percent change from baseline (min – max)	-14.0 (-91 – 72)	-59.0 (-100 – 86)	-18.0 (-100 – 158)	-56.0 (-100 – 88)
LS mean (95% CI)[b]	-16.8 (-20.6, -13.0)	-52.1 (-54.7, -49.4)	-16.0 (-22.2, -9.8)	-50.8 (-55.2, -46.4)
Treatment comparison (apremilast – placebo)				
Difference in LS means (2-sided 95% CI)[b]	--	-35.3 (-39.9, -30.6)	--	-34.8 (-42.4, -27.2)
2-sided p-value[b]	--	**< 0.0001**	--	**< 0.0001**

APR = apremilast; BID = twice daily; BSA = body surface area; CI = confidence interval; FAS = full analysis set; LOCF = Last observation carried forward; LS = least squares; min – max = minimum to maximum; PASI = Psoriasis Area and Severity Index; SD = standard deviation.

[a] Subjects with a baseline value and at least 1 postbaseline value are included.

[b] Based on an analysis of covariance model for the percent change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate. Means (LS means) and p values were adjusted by covariate. P-values in bold are considered statistically significant.

Note: Negative change indicates improvement.

Source: PSOR-008 CSR Table 31, PSOR-009 CSR Table 31.

Change in Pruritus VAS Score From Baseline at Week 16:

The subject population was highly pruritic at baseline, with a mean Pruritus VAS score ranging from about 65 to 68 mm in the treatment groups for the 2 studies. In both pivotal studies, subjects treated with APR 30 mg BID achieved a statistically significant improvement (reduction) in the Pruritus VAS score at Week 16 compared with placebo ($p < 0.0001$) (Table 45). The mean decrease of 31.5 mm for the APR 30 mg BID treatment group at Week 16 in Study PSOR-008 and the mean decrease of 33.5 mm in Study PSOR-009 represented about a 50% decrease in pruritus severity from baseline. In both studies, rapid and clinically meaningful responses were observed as early as Week 2 of APR 30 mg BID treatment based on differences (non-overlapping CIs) in the mean change in Pruritus VAS between treatment groups.

Table 45: Change in Pruritus VAS Score From Baseline at Week 16 in Studies PSOR-008 and PSOR-009 (FAS; LOCF)

Visit	PSOR-008		PSOR-009	
	Placebo (n = 282)	APR 30 BID (n = 562)	Placebo (n = 137)	APR 30 BID (n = 274)
Baseline, n[a]	277	559	133	268
Mean ± SD	65.2 ±24.79	66.2 ± 25.52	65.0 ± 25.96	67.8 ± 25.21
Median (min, max)	71.0 (1 – 100)	72.0 (0 – 100)	69.0 (3 – 100)	72.5 (1 – 100)
Week 16				
Mean ± SD	57.9 ± 29.60	34.7 ± 31.19	52.8 ± 33.29	34.3 ± 31.63
Median (min – max)	65.0 (1 – 100)	24.0 (0 – 100)	61.0 (0 – 100)	24.0 (0 – 100)
Mean change from baseline ± SD	-7.3 ± 27.08	-31.5 ± 32.43	-12.2 ± 30.94	-33.5 ± 35.46
Median change from baseline (min – max)	-3.0 (-95 – 72)	-31.0 (-99 – 76)	-6.0 (-97 – 66)	-34.0 (-100 – 59)
LS mean (95% CI)[b]	-7.3 (-10.9, -3.6)	-31.5 (-34.1, -29.0)	-12.2 (-18.0, -6.4)	-33.5 (-37.6, -29.4)
Treatment comparison (apremilast – placebo)				
Difference in LS means (2-sided 95% CI)[b]	--	-24.2 (-28.7, 19.8)	--	-21.3 (-28.4, -14.2)
2-sided p-value[b]	--	**< 0.0001**	--	**< 0.0001**

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; LOCF = Last observation carried forward; LS = least squares; min – max = minimum to maximum; SD = standard deviation; VAS = visual analog scale.

[a] Subjects with a baseline value and at least one postbaseline value are included.

[b] Based on an analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor (an analysis of variance model). Unadjusted means and p values are provided. P-values in bold are considered statistically significant.

Note: VAS values range from 0 to 100 mm. Higher scores correspond to poorer quality of life.

Source: PSOR-008 CSR Table 33, PSOR-009 CSR Table 33.

Change in DLQI Total Score from Baseline at Week 16

The mean DLQI Total Scores at baseline were approximately 12.5 in both pivotal studies, indicating a significant impact of psoriasis on the subjects' quality of life. In both studies, subjects treated with APR 30

mg BID achieved statistically significant improvement (reduction) in the DLQI Total Score at Week 16 compared with placebo (p <0.0001).

The mean changes from baseline were -2.1 and -6.6 for subjects treated with placebo or APR 30 mg BID, respectively, in Study PSOR-008 and were -2.8 and -6.7, respectively, in Study PSOR-009. The mean improvement at Week 16 for the APR 30 mg BID treatment group of 6.6 in Study PSOR-008, and 6.7 in Study PSOR-009, exceeded the Minimal Clinically Important Difference (MCID) of at least a 5-point decrease from baseline (Finlay, 1994; NICE, 2012).

The proportion of subjects achieving at least a 5-point decrease in DLQI in the placebo and APR 30 BID treatment groups were 33.5% and 70.2%, respectively, in Study PSOR-008, and were 42.9% and 70.8%, respectively, in Study PSOR-009.

Visual Analog Scales

Improvements in the subjects' self-assessment of various aspects of their disease as measured by VAS were observed in subjects treated with APR 30 mg BID compared to placebo at Week 16.

Subjects treated with APR 30 BID achieved nominally significant improvements (decreases) in both studies in the Skin Discomfort/Pain VAS score at Week 16 compared with placebo (nominal p <0.0001) (Table 46). The mean decreases of 28.3 mm and 28.5 mm for the APR 30 mg BID treatment group at Week 16 in Studies PSOR-008 and PSOR-009, respectively, represented about a 50% decrease in Skin Discomfort/Pain from baseline.

Subjects treated with APR 30 BID achieved nominally significant improvements (decreases) in both studies in Subject's Global Assessment of Psoriasis Disease Activity VAS score at Week 16 compared with placebo (nominal p <0.0001).

In Study PSOR-008, 20.5% of subjects entered study with PsA at baseline and in Study PSOR-009, 13.4% of subjects entered study with PsA at baseline. Subjects treated with APR 30 mg BID in Study PSOR-008 achieved nominally significant improvements in PsA Disease Activity.

VAS score at Week 16 compared with placebo (nominal p = 0.0033). The improvements (decreases) in Study PSOR-009 were numerically greater for the APR 30 BID treatment group compared with the placebo treatment group (p = 0.1618).

Table 46: Summary of Skin Discomfort/Pain VAS in Studies PSOR-008 and PSOR-009 for the Placebo-controlled Phase (Weeks 0 to 16; FAS; LOCF)

	PSOR-008		PSOR-009	
Visit	Placebo (n = 282)	APR 30 BID (n = 562)	Placebo (n = 137)	APR 30 BID (n = 274)
Baseline, n[a]	277	559	133	268
Mean ± SD	57.1 ± 29.65	58.1 ± 29.31	56.9 ± 28.89	58.9 ± 28.90
Week 16				
Mean change from baseline ± SD	-5.0 ± 28.99	-28.3 ± 32.45	-9.5 ± 30.78	-28.5 ± 34.45
Median change from baseline (min – max)	-1.0 (-86 – 74)	-24.0 (-98 – 86)	-3.0 (-95 – 55)	-24.5 (-99 – 81)
LS mean (95% CI)[b]	-5.0 (-8.7, -1.3)	-28.3 (-30.9, -25.7)	-9.5 (-15.2, -3.8)	-28.5 (-32.5, -24.5)
Treatment comparison (apremilast – placebo)				
Difference in LS means (2-sided 95% CI)[b]	--	-23.3 (-27.8, -18.7)	--	-19.0 (-25.9, -12.0)
2-sided p-value[b]	--	*< 0.0001*	--	*< 0.0001*

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; min – max = minimum to maximum; SD = standard deviation; VAS = Visual Analog Scale.

[a] The sample size (n) at baseline is based on all subjects with a baseline value. The sample size at a postbaseline time point (LOCF) is based on all subjects with a baseline value and at least one postbaseline value in the phase.

[b] Based on an analysis of covariance model for the change from baseline at Week 16. The model includes treatment group as a factor (an analysis of variance model). The unadjusted means and p-value are provided. P-values in italics are ≤ 0.050 and considered nominally significant based on hierarchical testing.

Notes: All values are LOCF unless otherwise noted. Skin Discomfort/Pain VAS scores ranges from 0 to 100 mm, where higher scores correspond to more skin discomfort/joint pain.

Source: PSOR-008 CSR Table 39, PSOR-009 CSR Table 39.

Health-related Quality of Life

Improvements in measures of quality of life were generally observed with APR 30 BID treatment compared to placebo at Week 16 in both studies.

Nail Assessments

Overall, 558 of the 844 subjects (66%) enrolled in Study PSOR-008 and 266 of the 411 subjects (64.7%) enrolled in Study PSOR-009 had nail psoriasis at baseline (Table 47). Among these subjects, a statistically significant improvement (reduction) in NAPSI score from baseline was detected in subjects treated with APR 30 BID at Week 16 compared with placebo (p <0.0001, Study PSOR-008, p = 0.0052, Study PSOR-009). The percent mean change from baseline at Week 16 for placebo-treated subjects was 6.5% and -7.1% in Studies PSOR-008 and PSOR-009, respectively, and for apremilast-treated subjects was -22.5% and -29.0% in Studies PSOR-008 and PSOR-009, respectively.

Table 47: Summary of Nail-related Analyses in Studies PSOR-008 and PSOR-009 for the Placebo-controlled Phase (Weeks 0 to 16; FAS With Baseline Nail Psoriasis Involvement ≥ 1; LOCF)

	PSOR-008		PSOR-009	
Endpoint	Placebo (n = 195)	APR 30 BID (n = 363)	Placebo (n = 91)	APR 30 BID (n = 175)
NAPSI Score at Week 16				
Baseline, n[a]	178	339	84	163
Mean ± SD	4.4 ± 2.14	4.3 ± 1.98	4.4 ± 2.02	4.2 ± 2.13
Week 16				
Mean % change from baseline ± SD	6.5 ± 60.57	-22.5 ± 54.86	-7.1 ± 46.64	-29.0 ± 67.47
Median % change from baseline (min – max)	0.0 (-100 – 200)	-25.0 (-100 – 200)	0.0 (-100 – 200)	-43.0 (-100 – 300)
LS mean (95% CI)[b]	6.5 (-1.8, 14.9)	-22.5 (-28.6, -16.5)	-6.4 (-19.4, 6.5)	-29.3 (-38.7, -20.0)
Treatment comparison (apremilast – placebo)				
Difference in LS means (2-sided 95% CI)[b]	--	-29.1 (-39.4, -18.7)	--	-22.9 (-38.9, -6.9)
2-sided p-value[b]	--	< 0.0001	--	0.0052

Scalp Psoriasis

Overall, 563 of the 844 subjects enrolled in Study PSOR-008 and 269 of the 411 subjects enrolled in Study PSOR-009 had moderate or more severe scalp psoriasis at Baseline (ScPGA ≥3). Among these subjects, a statistically significantly greater proportion of subjects treated with APR 30 mg BID achieved an ScPGA score of 0 or 1 (clear or minimal) at Week 16 compared with placebo (p <0.0001) in both pivotal studies (Table 48).

The proportion of subjects with an ScPGA score of 0 or 1 (clear or minimal) were 17.5% and 46.5% for placebo and APR 30 mg BID treatment groups, respectively, in Study PSOR-008 and were 17.2% and 40.9%, respectively in Study PSOR-009. A nominally significantly greater proportion of subjects treated with APR 30 mg BID achieved improvements in the ScPGA score of 0, 1, or 2 (clear, minimal, or mild) at Week 16 compared with placebo (nominal p <0.0001) in both studies.

The response rates for a ScPGA score of 0, 1, or 2 (clear, minimal, or mild) were 35.4% and 68.7% for placebo and APR 30 mg BID treatment groups, respectively, in Study PSOR-008 and were 41.9% and 67.0%, respectively in Study PSOR-009.

Table 48: Summary of Scalp Psoriasis-related Analyses in Studies PSOR-008 and PSOR-009 for the Placebo-controlled Phase (Weeks 0 to 16; FAS With ScPGA ≥ 3 at Baseline; LOCF)

Endpoint	PSOR-008		PSOR-009	
	Placebo (n = 189)	APR 30 BID (n = 374)	Placebo (n = 93)	APR 30 BID (n = 176)
Week 16 ScPGA Score of 0 or 1				
n[a] (%)	33 (17.5)	174 (46.5)	16 (17.2)	72 (40.9)
Treatment comparison (apremilast – placebo)				
Difference in proportions (2-sided 95% CI)[b]	-	29.1 (21.7, 36.5)		23.7 (13.1, 34.3)
2-sided p-value[b]	-	**< 0.0001**		**< 0.0001**
Week 16 ScPGA Score of 0, 1, or 2				
n[c] (%)	67 (35.4)	257 (68.7)	39 (41.9)	118 (67.0)
Treatment comparison (apremilast – placebo)				
Difference in proportions (2-sided 95% CI)[b]	-	33.3 (25.0, 41.5)		25.1 (12.9, 37.3)
2-sided p-value[b]	-	*< 0.0001*		*< 0.0001*

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; ScPGA = Scalp Physician Global Assessment.

[a] The sample size (n) is based on subjects with ScPGA ≥ 3 at baseline and response includes scores of 0 or 1.

[b] Two-sided 95% CI is based on the normal approximation. Two-sided p-value is based on the two-sided chi-square test. P-values in italics are ≤ 0.050 and considered nominally significant based on hierarchical testing.

[c] The sample size (n) is based on subjects with ScPGA ≥ 3 and response includes improvement from baseline score 3 or above to 0, 1 or 2, from 2 to 0 or 1, or from 1 to 0.

Note: The 6-point ScPGA scores range from 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe), to 5 (very severe). LOCF values were used for missing Week 16 values.

Source: PSOR-008 CSR Table 42, PSOR-009 Table 42.

Palmoplantar Psoriasis

A total of 83 subjects in Study PSOR-008 and 42 subjects in Study PSOR-009 had moderate or severe palmoplantar psoriasis (PPPGA Score of 3 or 4 [moderate or severe]) at baseline.

Among subjects with a PPPGA baseline score ≥3 (moderate or greater) in Study PSOR-008, a larger proportion of subjects treated with APR 30 mg BID showed improvement in the palmoplantar psoriasis (PPPGA score to 0 or 1[clear or almost clear]) compared with placebo (Table 49). This difference was numerically greater in Study PSOR-008 (p = 0.4912) and nominally significantly greater in Study PSOR-009 (nominal p = 0.0315).

Table 49: Summary of Palmoplantar Psoriasis Analyses in Studies PSOR-008 and PSOR-009 for the Placebo-controlled Phase (Weeks 0 to 16; FAS With Baseline PPPGA ≥ 3; LOCF).

Endpoint	PSOR-008		PSOR-009	
	Placebo (n = 26)	APR 30 BID (n = 57)	Placebo (n = 16)	APR 30 BID (n = 26)
Week 16 PPPGA Score of 0 or 1, n (%)[a]	8 (30.8)	22 (38.6)	5 (31.3)	17 (65.4)
Treatment comparison (apremilast – placebo)				
Difference in proportions (2-sided 95% CI)[b]	--	7.8 (-14.0, 29.6)	--	34.1 (5.0, 63.3)
2-sided p-value[b]	--	0.4912	--	*0.0315*

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; PPPGA = Palmoplantar Psoriasis Physician Global Assessment.

[a] The sample size (n) is based on subjects in the FAS population with improvement from a PPPGA baseline score of 3 or above to 0 or 1.

[b] Two-sided 95% CI is based on the normal approximation. Two-sided p-value is based on the two-sided chi-square test. P-values in italics are ≤ 0.050 and considered nominally significant based on hierarchical testing.

Note: The 5-point PPPGA scores range from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe). A subject who had no score at a time point is counted as a nonresponder.

Source: PSOR-008 CSR Table 43, PSOR-009 CSR Table 43.

Maintenance Phase (Weeks 16 to 32)

Psoriasis Area and Severity Index

For both studies, the PASI-75 response rates for subjects originally randomized to APR 30 mg BID peaked around Week 16 and were generally maintained through Week 32. Subjects originally randomized to placebo demonstrated a response to apremilast treatment, similar to that seen for subjects originally randomized to APR 30 mg BID at baseline. By Week 24, the PASI response rates for subjects who were

originally randomized to placebo following 8 weeks of APR 30 BID treatment were generally comparable to those for subjects receiving 24 weeks of APR 30 mg BID.

By Week 32, the PASI response rates for subjects who were originally randomized to placebo following 16 weeks of APR 30 BID treatment were also generally comparable to those for subjects receiving 32 weeks of APR 30 BID (Table 50).

Table 50: PASI Score Analyses During the Maintenance Phase (Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS)

Endpoint Visit	PSOR-008		PSOR-009	
	Placebo/ APR 30 BID (n = 245)[a]	APR 30 BID/ APR 30 BID (n = 562)[b]	Placebo/ APR 30 BID (n = 108)[a]	APR 30 BID/ APR 30 BID (n = 274)[b]
PASI-50				
Week 24, n (%) [95% CI][c,d]	143 (58.4) [51.9, 64.6]	322 (57.3) [53.1, 61.4]	67 (62.0) [52.2, 71.2]	137 (50.0) [43.9, 56.1]
Week 32, n (%) [95% CI][c,d]	156 (63.7) [57.3, 69.7]	301 (53.6) [49.3, 57.7]	71 (65.7) [56.0, 74.6]	126 (46.0) [40.0, 52.1]
PASI-75				
Week 24, n (%) [95% CI][c,d]	59 (24.1) [18.9, 29.9]	175 (31.1) [27.3, 35.1]	28 (25.9) [18.0, 35.2]	74 (27.0) [21.8, 32.7]
Week 32, n (%) [95% CI][c,d]	76 (31.0) [25.3, 37.2]	159 (28.3) [24.6, 32.2]	31 (28.7) [20.4, 38.2]	68 (24.8) [19.8, 30.4]
PASI-90				
Week 24, n (%) [95% CI][c,d]	16 (6.5) [3.8, 10.4]	68 (12.1) [9.5, 15.1]	8 (7.4) [3.3, 14.1]	25 (9.1) [6.0, 13.2]
Week 32, n (%) [95% CI][c,d]	22 (9.0) [5.7, 13.3]	68 (12.1) [9.5, 15.1]	9 (8.3) [3.9, 15.2]	26 (9.5) [6.3, 13.6]
Percent change in PASI score from baseline				
Baseline, n[e]	245	562	108	274
Mean ± SD	19.01 ± 7.132	18.74 ± 7.182	19.44 ± 6.853	18.93 ± 7.058
Median (min – max)	17.20 (12.0 – 59.3)	16.60 (12.0 – 60.0)	17.65 (12.0 – 53.3)	16.55 (12.0 – 57.8)
Week 24, n[e]	236	475	103	222
Mean % change from baseline ± SD	-54.7 ± 25.41	-60.4 ± 27.40	-54.1 ± 29.40	-56.6 ± 30.56
Median % change from baseline (min – max)	-58.5 (-100 – 35)	-65.0 (-100 – 55)	-57.0 (-100 – 46)	-65.0 (-100 – 70)
2-sided 95% CI for mean	(-58.0, -51.5)	(-62.9, -57.9)	(-59.9, -48.4)	(-60.7, -52.6)
Week 32, n[e]	216	425	98	191
Mean % change from baseline ± SD	-62.2 ± 23.71	-61.9 ± 27.75	-59.8 ± 27.52	-58.8 ± 28.44
Median % change from baseline (min – max)	-63.5 (-100 – 26)	-67.0 (-100 – 61)	-61.5 (-100 – 77)	-64.0 (-100 – 50)
2-sided 95% CI for mean	(-65.4, -59.1)	(-64.6, -59.3)	(-65.4, -54.3)	(-62.8, -54.7)

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; min – max = minimum to maximum; PASI = Psoriasis Area and Severity Index; SD = standard deviation.

[a] Subjects in the FAS population who were initially randomized to placebo and who crossed to APR 30 BID at Week 16.

[b] Subjects in the FAS population who were initially randomized to APR 30 BID at baseline.

[c] Two-sided 95% CI is based on the Clopper-Pearson method.

[d] Subjects who discontinued prior to a visit or whose PASI evaluations were missing at a visit were counted as nonresponders.

[e] Sample size (n) is based on subjects with a baseline value and a postbaseline value at the study week.

Source: PSOR-008 CSR Table 45, PSOR-008 CSR Table 14.2.1.2.4, PSOR-009 CSR Table 45, PSOR-009 CSR Table 14.2.1.2.4.

Static Physician Global Assessment:

The sPGA response rates for subjects originally randomized to APR 30 mg BID peaked around Week 16 in both studies and were generally maintained through Week 32. Subjects originally randomized to placebo demonstrated rapid sPGA response following initiation of apremilast treatment, similar to that seen for subjects originally randomized to APR 30 mg BID at baseline.

By Week 24, the response rates for subjects originally randomized to placebo following 8 weeks of APR 30 BID treatment were similar to those for subjects who received 24 weeks of APR 30 BID (Table 51).

Table 51: Proportion of Subjects Achieving an sPGA Response During the Maintenance Phase (Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS)

Endpoint Visit	PSOR-008		PSOR-009	
	Placebo/ APR 30 BID[a] (n = 245)	APR 30 BID/ APR 30 BID[b] (n = 562)	Placebo/ APR 30 BID[a] (n = 108)	APR 30 BID/ APR 30 BID[b] (n = 274)
sPGA Response[c]				
Week 24				
n (%) [95% CI][d]	44 (18.0) [13.4, 23.3]	140 (24.9) [21.4, 28.7]	18 (16.7) [10.2, 25.1]	53 (19.3) [14.8, 24.5]
Week 32				
n (%) [95% CI][d]	62 (25.3) [20.0, 31.2]	135 (24.0) [20.5, 27.8]	25 (23.1) [15.6, 32.2]	49 (17.9) [13.5, 22.9]

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; sPGA = static Physician Global Assessment.
[a] Subjects in the FAS population who were initially randomized to placebo and who crossed to APR 30 BID at Week 16.
[b] Subjects in the FAS population who were initially randomized to APR 30 BID at baseline.
[c] An sPGA response is defined as an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.
[d] Two-sided 95% CI is based on the Clopper-Pearson method.
Source: PSOR-008 CSR Table 46, PSOR-009 CSR Table 46.

Body Surface Area Involvement

At Week 32, after placebo subjects had been treated with APR 30 BID for 16 weeks, reductions in BSA involvement were similar between the treatment groups, and greater than the changes at Week 16. The mean percent changes (improvement) from baseline in BSA involvement for the placebo/APR 30 mg BID and APR 30 mg BID/APR 30 BID treatment groups were -59.25% and -61.18%, respectively, in Study PSOR-008 and -58.73% and -60.67%, respectively, in Study PSOR-009 (Table 52).

Table 52: Percent Change From Baseline in Psoriasis Affected BSA During the Maintenance Phase (Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS)

Visit	PSOR-008		PSOR-009	
	Placebo/ APR 30 BID[a] (n = 245)	APR 30 BID/ APR 30 BID[b] (n = 562)	Placebo/ APR 30 BID[a] (n = 108)	APR 30 BID/ APR 30 BID[b] (n = 274)
Baseline, n[c]	245	562	108	274
Mean ± SD	24.62 ± 14.092	24.40 ± 14.716	26.68 ± 15.430	25.46 ± 15.416
Median (min – max)	21.00 (10.0 – 84.0)	20.00 (9.0 – 86.0)	22.00 (10.0 – 78.0)	21.00 (10.0 – 86.0)
Week 24, n[c]	236	475	103	222
Mean % change from baseline ± SD	-42.57 ± 35.674	-58.98 ± 33.594	-43.39 ± 42.174	-56.57 ± 36.660
Median % change from baseline (min – max)	-46.83 (-100.0 – 81.0)	-66.00 (-100.0 – 128.6)	-51.43 (-100 – 103.2)	-67.22 (-100 – 110.0)
2-sided 95% CI for mean	(-47.15, -38.00)	(-62.01, -55.95)	(-51.63, 35.14)	(-61.42, -51.72)
Week 32, n[c]	216	424	98	191
Mean % change from baseline ± SD	-59.25 ± 30.843	-61.18 ± 34.196	-58.73 ± 38.198	-60.67 ± 33.528
Median % change from baseline (min – max)	-64.29 (-100.0 – 81.0)	-68.96 (-100.0 – 128.6)	-68.38 (-100 – 110.5)	-68.75 (-100 – 42.6)
2-sided 95% CI for mean	(-63.39, -55.12)	(-64.44, -57.91)	(-66.38, -51.07)	(-65.45, -55.88)

APR = apremilast; BID = twice daily; BSA = body surface area; CI = confidence interval; FAS = full analysis set; min – max = minimum to maximum; SD = standard deviation.
[a] Subjects in the FAS population who were initially randomized to placebo and who crossed to APR 30 BID at Week 16.
[b] Subjects in the FAS population who were initially randomized to APR 30 BID at baseline.
[c] The sample size (n) at baseline (Week 0) is based on all included subjects with a baseline value. The sample size at a postbaseline time point (observed data) is based on subjects with a baseline value and a postbaseline value at the time point.
Source: PSOR-008 CSR Table 47, PSOR-008 CSR Table 14.2.3.2, PSOR-009 CSR Table 47, PSOR-009 CSR Table 14.2.3.2.

Dermatology Life Quality Index

At Weeks 24 and 32 in both studies, subjects originally randomized to placebo achieved similar changes in DLQI Total Scores from baseline as did those subjects originally randomized to APR 30 mg BID (Table 53) and were greater than the changes observed at Week 16 (Table 54). Among subjects with a baseline DLQI Total Score >5, the proportion of subjects who achieved a decrease (improvement) of at least 5 points from baseline (MCID; Finlay, 1994; NICE, 2012) at Weeks 24 and 32 was similar between the treatment groups in Study PSOR-008 (approximately60% of subjects). In the APR 30 BID/APR 30 BID treatment group in Study PSOR-009, 59.3% and 50.9% of subjects achieved a decrease (improvement) of at least 5 points from baseline in DLQI Total Score (MCID) at Weeks 24 and 32, respectively, and in the placebo/APR 30 BID treatment group, 72.8% and 65.2% of subjects achieved at least a 5-point decrease in DLQI Total Score at Weeks 24 and 32, respectively.

Table 53: Change From Baseline in DLQI Total Score During the Maintenance Phase (Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS)

Table 54: Proportion of Subjects Who Achieved a Decrease of at Least 5 Points in DLQI Total Score During the Maintenance Phase Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS)

Endpoint Visit	PSOR-008		PSOR-009	
	Placebo/ APR 30 BID[a] (n = 245)	APR 30 BID/ APR 30 BID[b] (n = 562)	Placebo/ APR 30 BID[a] (n = 108)	APR 30 BID/ APR 30 BID[b] (n = 274)
Subjects with ≥ 5-point decrease in DLQI Total Score, n (%)	206	459	92	226
Week 24 n (%) [95% CI][c]	132 (64.1) [57.1, 70.6]	284 (61.9) [57.3, 66.3]	67 (72.8) [62.6, 81.6]	134 (59.3) [52.6, 65.8]
Week 32 n (%) [95% CI][c]	120 (58.3) [51.2, 65.1]	264 (57.5) [52.8, 62.1]	60 (65.2) [54.6, 74.9]	115 (50.9) [44.2, 57.6]
Subjects with ≥ 5-point decrease in DLQI Total Score and achieving PASI-50, n	206	459	92	226
Week 24 n (%) [95% CI][c]	86 (41.7) [34.9, 48.8]	216 (47.1) [42.4, 51.7]	49 (53.3) [42.6, 63.7]	98 (43.4) [36.8, 50.1]
Week 32 n (%) [95% CI][c]	94 (45.6) [38.7, 52.7]	197 (42.9) [38.3, 47.6]	50 (54.3) [43.6, 64.8]	83 (36.7) [30.4, 43.4]

APR = apremilast; BID = twice daily; CI = confidence interval; DLQI = Dermatology Life Quality Index; FAS = full analysis set; min – max = minimum to maximum; PASI = Psoriasis Area and Severity Index.
[a] Subjects in the FAS population who were initially randomized to placebo and who crossed to APR 30 BID at Week 16.
[b] Subjects in the FAS population who were initially randomized to APR 30 BID at baseline.
[c] Two-sided 95% CI is based on the Clopper-Pearson method.
Note: The DLQI Total Score has a possible range of 0 to 30, where higher scores correspond to poorer quality of life.
Source: PSOR-008 CSR Table 48, PSOR-009 CSR Table 49.

Visual Analog Scales

During the Maintenance Phase (Weeks 16 to 32), improvements in VAS-related endpoints were generally maintained in subjects who continued to receive apremilast (APR 30 BID/APR 30 BID). Subjects who were originally randomized to placebo at Week 0 and transitioned to APR 30 BID at Week 16 (placebo/APR 30 BID) achieved similar responses to those observed in subjects randomized to apremilast at the baseline visit (APR 30 BID/APR 30 BID) and treated for 32 weeks. These responses were evident beginning at Week 24, following 8 weeks of apremilast therapy (Table 55).

At Weeks 24 and 32, subjects in the placebo/APR 30 BID treatment groups achieved similar improvements (decreases) in the Pruritus VAS compared with subjects in the APR 30 BID/APR 30 BID treatment group, with mean decreases of approximately 30 mm or greater in both studies. Similar improvements in the Skin Discomfort/Pain VAS (mean decreases of approximately 30 mm) were observed in both the placebo/APR 30 BID and APR 30 BID/APR 30 BID treatment group.

In both studies, the pruritus and skin discomfort/pain responses in subjects originally randomized to APR 30 BID were observed by Week 2, plateaued by about Week 8, and were maintained through Week 32.

Subjects originally randomized to placebo demonstrated a similar rapid improvement in pruritus and skin discomfort/pain following initiation of apremilast treatment at Week 16, which was also maintained through Week 32.

Table 55: Pruritus VAS and Skin Discomfort/Pain VAS During the Maintenance Phase (Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS)

Endpoint Visit	PSOR-008		PSOR-009	
	Placebo/ APR 30 BID[a] (n = 245)	APR 30 BID/ APR 30 BID[b] (n = 562)	Placebo/ APR 30 BID[a] (n = 108)	APR 30 BID/ APR 30 BID[b] (n = 274)
Pruritus VAS				
Baseline, n[c]	245	562	108	274
Mean ± SD	64.8 ± 24.85	66.1 ± 25.55	62.5 ± 26.33	67.7 ± 25.31
Median (min – max)	71.0 (1 – 100)	72.0 (0 – 100)	64.0 (3 – 100)	72.0 (1 – 100)
Week 24, n[c]	237	475	102	220
Mean change from baseline ± SD	-34.8 ± 28.32	-33.8 ± 31.77	-32.7 ± 32.76	-33.1 ± 35.06
Median change from baseline (min – max)	-33.0 (-96 – 34)	-33.0 (-99 – 61)	-31.0 (-99 – 58)	-35.5 (-98 – 62)
2-sided 95% CI for mean	(-38.4, -31.1)	(-36.7, -31.0)	(-39.2, -26.3)	(-37.8, -28.5)
Week 32, n[c]	216	424	98	191
Mean change from baseline ± SD	-33.9 ± 29.08	-34. 5 ± 31.16	-35.2 ± 32.38	-34.7 ± 32.80
Median change from baseline (min – max)	-32.0 (-98 – 44)	-34.5 (-98 – 73)	-39.0 (-98 – 41)	-36.0 (-99 – 47)
2-sided 95% CI for mean	(-37.8, -30.0)	(-37.5, -31.5)	(-41.6, -28.7)	(-39.4, -30.0)
Skin discomfort/pain VAS				
Baseline, n[c]	245	562	108	274
Mean ± SD	56.3 ± 29.83	58.0 ± 29.40	54.5 ± 28.73	58.7 ± 29.17
Median (min – max)	65.0 (0 – 100)	66.0 (0 – 100)	58.0 (0 – 100)	65.5 (0 – 100)
Week 24, n[c]	237	475	102	220
Mean change from baseline ± SD	-29.9 ± 30.26	-30.2 ± 32.18	-30.2 ± 30.62	-30.2 ± 35.71
Median change from baseline (min – max)	-28.0 (-92 – 49)	-28.0 (-98 – 95)	-25.5 (-99 – 40)	-28.0 (-99 – 85)
2-sided 95% CI for mean	(-33.8, -26.0)	(-33.1, -27.3)	(-36.2, -24.2)	(-35.0, -25.5)
Week 32, n[c]	216	424	98	191
Mean change from baseline ± SD	-29.0 ± 31.63	-30.0 ± 31.85	-31.4 ± 32.94	-28.6 ± 34.13
Median change from baseline (min – max)	-26.0 (-94 – 80)	-27.0 (-98 – 94)	-25.5 (-98 – 50)	-27.0 (-99 – 70)
2-sided 95% CI for mean	(-33.2, -24.7)	(-33.0, 27.0)	(-38.0, -24.8)	(-33.5, -23.8)

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; min – max = minimum to maximum; SD = standard deviation; VAS = Visual Analog Scale.

[a] Subjects in the FAS population who were initially randomized to placebo and who crossed to APR 30 BID at Week 16.

[b] Subjects in the FAS population who were initially randomized to APR 30 BID at baseline.

[c] The sample size (n) at baseline (Week 0) is based on all included subjects with a baseline value. The sample size at a postbaseline time point (observed data) is based on subjects with a baseline value and a postbaseline value at the time point. The sample size at the end of phase is based on subjects with a baseline value and a value in the phase.

Note: Pruritus VAS scores range from 0 to 100 mm where higher scores correspond to worse pruritus (itch). Skin Discomfort/Pain VAS scores range from 0 to 100 mm, where higher scores correspond to more skin discomfort/joint pain.

Source: PSOR-008 CSR Table 49, PSOR-008 CSR Table 14.2.4.2.1.1, PSOR-008 CSR Table 14.2.4.2.2.1, PSOR-009 CSR Table 50, PSOR-009 CSR Table 14.2.4.2.1.1, PSOR-009 CSR Table 14.2.4.2.2.1.

Health-related Quality of Life

Overall, improvements in health-related quality of life assessments were observed with apremilast treatment at Weeks 24 and 32. In both studies, subjects originally randomized to placebo at baseline and treated with APR 30 BID beginning at Week 16 achieved similar improvements (increases) in SF-36v2 MCS by Weeks 24 and 32 as subjects originally randomized to APR 30 mg BID. At Weeks 24 and 32, the mean changes for the APR 30 BID/APR 30 BID treatment group exceeded the MCID of 2.5 in Study PSOR-008, and the mean changes for both treatment groups (placebo/APR 30 BID and APR 30 BID/APR 30 BID) reached or exceeded the MCID of 2.5 in Study PSOR-009.

Improvements in SF-36v2 PCS Scores reached or exceeded the MCID of 2.5 for the placebo/APR 30 BID treatment group in Study PSOR-009 at Weeks 24 and 32.

In the APR 30 BID/APR 30 BID treatment group, improvements (decreases) in PHQ-8 Total

Scores were generally maintained at Weeks 24 and 32. In the placebo/APR 30 BID treatment group, improvements (decreases) in PHQ-8 Total Score were evident by Week 24 and continued through Week 32.

Nail Assessments

In both studies, subjects originally randomized to APR 30 BID who had nail involvement at baseline achieved a greater improvement (reduction in total score) in overall NAPSI score at Weeks 24 and 32

compared with subjects originally randomized to placebo and then treated with APR 30 BID (Table 56). In addition, the subjects originally randomized to APR 30 BID achieved even better (lower) NAPSI scores at Weeks 24 and 32 than at Week 16. This is expected, as longer treatment periods allow for a greater outgrowth of healthy nails leading to improved NAPSI scores. As such, the lower scores for subjects originally randomized to placebo are probably due to the shorter time on active treatment. In addition, a greater proportion of subjects originally randomized to APR 30 BID achieved a NAPSI-50 at Weeks 24 and 32 compared with subjects originally randomized to placebo. At Weeks 24 and 32, subjects originally randomized to APR 30 BID achieved a larger decrease in the number of involved nails, compared with subjects originally randomized to placebo.

Table 56: Nail Psoriasis Analyses During the Maintenance Phase (Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS With Baseline Nail Psoriasis Involvement ≥ 1)

Endpoint Visit	PSOR-008		PSOR-009	
	Placebo/ APR 30 BID[a] (n = 172)	APR 30 BID/ APR 30 BID[b] (n = 363)	Placebo/ APR 30 BID[a] (n = 75)	APR 30 BID/ APR 30 BID[b] (n = 175)
Overall NAPSI Score				
Week 24, n[c]	162	303	71	147
Mean % change from baseline ± SD	-11.2 ± 72.71	-42.1 ± 52.58	-24.9 ± 43.46	-42.6 ± 61.4
Median % change from baseline (min – max)	-20.0 (-100 – 300)	-50 (-100 – 200)	-25.0 (-100 – 100)	-50.0 (-100 – 300)
2-sided 95% CI for mean	(-22.4, 0.1)	(-48.0, -36.1)	(-35.1, -14.6)	(-52.6, -32.6)
Week 32, n[c]	145	275	68	134
Mean % change from baseline ± SD	-24.6 ± 65.54	-43.6 ± 56.84	-47.6 ± 40.55	-60.0 ± 55.74
Median % change from baseline (min – max)	-33.0 (-100 – 300)	-50 (-100 – 200)	-50.0 (-100 – 100)	-75.0 (-100 – 300)
2-sided 95% CI for mean	(-35.4, -13.9)	(-50.3, -36.8)	(-57.4, -37.8)	(-69.5, -50.5)

Scalp Psoriasis

Of the subjects with ScPGA score ≥ 3 (moderate or greater) at baseline, the proportion of subjects who achieved an improvement of ScPGA score of 0 or 1 (clear or minimal) was numerically greater for the placebo/APR 30 BID group than for the APR 30 BID/APR 30 BID group at Weeks 24 and 32 (Table 57).

The differences between the treatment groups were greater for Study PSOR-009 than Study PSOR-008. Similar findings were observed for subjects who achieved an improvement of ScPGA score of 0, 1, or 2 (clear, minimal, or mild).

Table 57: Scalp Psoriasis Analyses During the Maintenance Phase (Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS With Baseline ScPGA ≥ 3)

Endpoint Visit	PSOR-008		PSOR-009	
	Placebo/ APR 30 BID[a] (n = 163)	APR 30 BID/ APR 30 BID[b] (n = 374)	Placebo/ APR 30 BID[a] (n = 71)	APR 30 BID/ APR 30 BID[b] (n = 176)
ScPGA Score of 0 or 1[c]				
Wk 24 n (%) [95% CI][d]	72 (44.2) [36.4, 52.1]	165 (44.1) [39.0, 49.3]	35 (49.3) [37.2, 61.4]	60 (34.1) [27.1, 41.6]
Wk 32 n (%) [95% CI][d]	71 (43.6) [35.8, 51.5]	140 (37.4) [32.5, 42.6]	36 (50.7) [38.6, 62.8]	57 (32.4) [25.5, 39.8]
ScPGA Score of 0, 1, or 2[e]				
Wk 24 n (%) [95% CI][d]	118 (72.4) [64.9, 79.1]	231 (61.8) [56.6, 66.7]	51 (71.8) [59.9, 81.9]	98 (55.7) [48.0, 63.2]
Wk 32 n (%) [95% CI][d]	109 (66.9) [59.1, 74.0]	211 (56.4) [51.2, 61.5]	53 (74.6) [62.9, 84.2]	90 (51.1) [43.5, 58.7]

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; ScPGA = Scalp Physician Global Assessment; Wk = week.
[a] Subjects in the FAS population with moderate or greater scalp psoriasis at baseline who were initially randomized to placebo and who crossed to APR 30 BID at Week 16.
[b] Subjects in the FAS population with moderate or greater scalp psoriasis at baseline who were initially randomized to APR 30 BID at baseline.
[c] Response includes improvement from baseline score 3 or above to 0 or 1.
[d] Two-sided 95% CI based on the Clopper-Pearson method.
[e] Response includes improvement from baseline score 3 or above to 0, 1, or 2.
Note: The 6-point ScPGA scores range from 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe), to 5 (very severe). A subject who had no score at a time point is counted as a nonresponder.
Source: PSOR-008 CSR Table 52, PSOR-009 CSR Table 53.

Palmoplantar Psoriasis

Of the subjects with a PPPGA score ≥3 (moderate or greater) at baseline, the proportion of subjects who achieved an improvement of PPPGA score of 0 or 1 (clear or almost clear) was numerically greater for the placebo/APR 30 BID group than for the APR 30 BID/APR 30 BID group at Weeks 24 and 32 (Table 58).

Table 58: Palmoplantar Psoriasis Analyses During the Maintenance Phase (Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS With Baseline PPPGA ≥ 3)

Endpoint Visit	PSOR-008		PSOR-009	
	Placebo/ APR 30 BID[a] (n = 27)	APR 30 BID/ APR 30 BID[b] (n = 57)	Placebo/ APR 30 BID[a] (n = 13)	APR 30 BID/ APR 30 BID[b] (n = 26)
PPPGA Score of 0 or 1[c]				
Wk 24 n (%) [95% CI][d]	12 (52.2) [30.6, 73.2]	27 (47.4) [34.0, 61.0]	8 (61.5) [31.6, 86.1]	14 (53.8) [33.4, 73.4]
Wk 32 n (%) [95% CI][d]	13 (56.5) [34.5, 76.8]	24 (42.1) [29.1, 55.9]	9 (69.2) [38.6, 90.9]	14 (53.8) [33.4, 73.4]

APR = apremilast; BID = twice daily; CI = confidence interval; FAS = full analysis set; ScPGA = Scalp Physician Global Assessment; Wk = week.
[a] Subjects in the FAS population with moderate or greater palmoplantar psoriasis at baseline who were initially randomized to placebo and who crossed to APR 30 BID at Week 16.
[b] Subjects in the FAS population with moderate or greater palmoplantar psoriasis at baseline who were initially randomized to APR 30 BID at baseline.
[c] Response includes improvement from baseline score 3 or above to 0 or 1.
[d] Two-sided 95% CI based on the Clopper-Pearson method.
Note: The 5-point palmoplantar psoriasis physician global assessment (PPPGA) scores range from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe). Subject who had no score at a time point is counted as a nonresponder.
Source: PSOR-008 CSR Table 53, PSOR-009 CSR Table 54.

Randomized Treatment Withdrawal Phase (Weeks 32 to 52).

Subjects who were re-randomized were those subjects originally randomized to APR 30 mg BID and achieved a PASI-75 response (Study PSOR-008) or at least a PASI-50 response (Study PSOR-009) at Week 32 , were re-randomized to either APR 30 mg BID or placebo in order to evaluate time to first loss of effect.

Subjects who were not re-randomized were those subjects originally randomized to APR 30 BID and did not achieve a PASI-75 response (Study PSOR-008) or at least a PASI-50 response (Study PSOR-009) at Week 32 or were those subjects originally randomized to placebo (regardless of response). In Study PSOR-008, there were 4 subjects originally randomized to APR 30 mg BID who achieved a PASI-75 response who were not re randomized at Week 32.In Study PSOR-009, there was one subject originally randomized to APR 30 BID who achieved a PASI-50 response who was not re randomized at Week 32.

Additionally, non responders (<PASI-50) in both studies and partial responders in Study PSOR-008 (PASI-50 to PASI-74) had the option of adding topical medications and/or UVB rescue therapy beginning at Week 32 at the discretion of the investigator.

Time to First Loss of PASI-75 Response (Loss of Effect in Study PSOR-008)

The time to first loss of effect was defined in Study PSOR-008 as the time when loss of PASI-75 response first occurred after re randomization in the Randomized Treatment Withdrawal Phase (Figure 11). In the Randomized Treatment Withdrawal Phase, 77 subjects were re-randomized to placebo (APR 30 BID/APR 30 BID/placebo) and 77 subjects were re randomized to APR 30 BID (APR 30 BID/APR 30 BID/APR 30 BID) at Week 32.

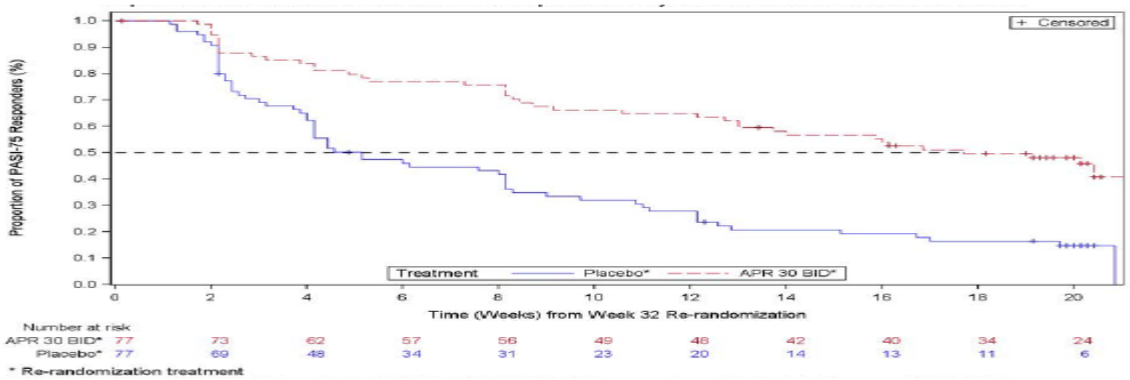
Of the re-randomized subjects in the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment group, 63/77 subjects (81.8%) and 40/77 subjects (51.9%), respectively, lost PASI-75 response at some time point during the Randomized Treatment Withdrawal Phase.

The number of censored subjects (those subjects whose time to loss of PASI-75 could not be determined or who did not lose PASI-75 prior to Week 52) was 14 (18.2%) and 37 (48.1%) in the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively

For the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, the median time to first loss of PASI-75 was 5.1 weeks and 17.7 weeks from the Week 32 re randomization, respectively (nominal p < 0.0001).

Some subjects on APR 30 BID/APR 30 BID/APR 30 BID regained PASI-75 at later time points following loss of the response.

Figure 11 - Time to First Loss of PASI-75 Response During the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) in Study PSOR-008



APR = apremilast; BID = twice daily; PASI = Psoriasis Area and Severity Index.
Note: Subjects were censored after the addition of topical/photo or other effective psoriasis therapies.
Source: PSOR-008 CSR Figure 12.

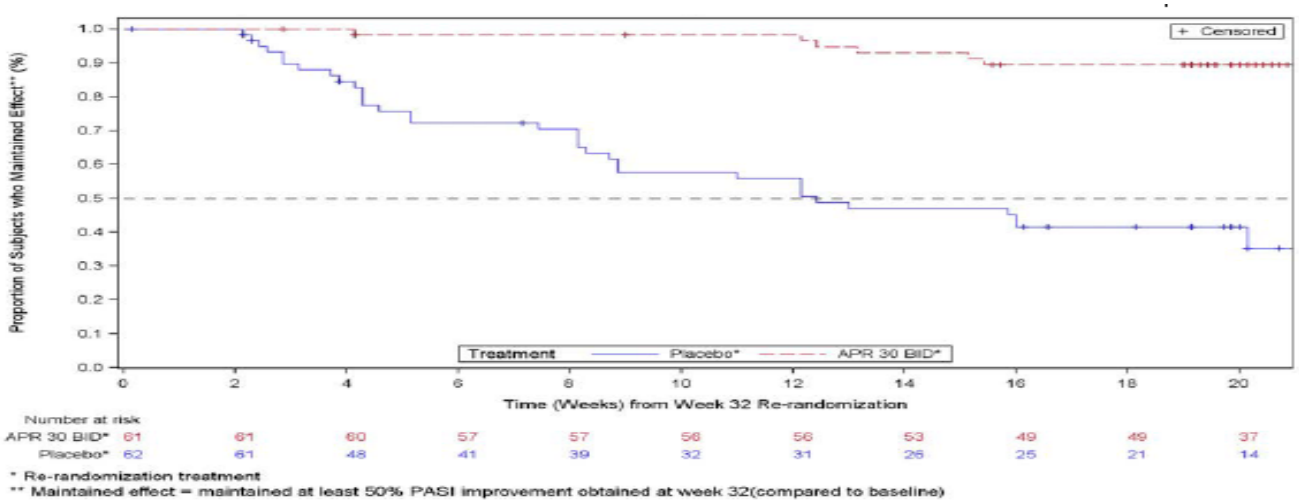
Time to First Loss of 50% Improvement of PASI Score (Loss of Effect in Study PSOR-009).

In contrast to PSOR-008, the time to first loss of effect in Study PSOR-009 was defined as loss of 50% of the improvement in PASI score obtained at Week 32 compared to baseline after re randomization in the Randomized Treatment Withdrawal Phase (Figure 12). Subjects eligible to be re-randomized were ≥PASI-50 responders. In the Randomized Treatment Withdrawal Phase, 62 subjects were re-randomized to placebo (APR 30 BID/APR 30 BID/placebo) and 61 subjects were re randomized to APR 30 BID (APR 30 BID/APR 30 BID/APR 30 BID) at Week 32.

For the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively, 35/62 subjects (56.5%) and 7/61 subjects (11.5%) lost 50% of their Week 32 PASI improvement at some time point during the Randomized Treatment Withdrawal Phase. The number of censored subjects (those subjects where time to loss of 50% of their PASI improvement could not be determined or who did not lose 50% of their PASI improvement prior to Week 52) was 27 (43.5%) and 54 (88.5%) in the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively

The median time to a loss of 50% of the improvement in PASI score obtained at Week 32 compared to baseline was 12.4 and 21.9 weeks following the Week 32 re-randomization for the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively (nominal p < 0.0001).

Figure 12 - Time to First Loss of 50% of PASI Improvement During the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) in Study PSOR-009



APR = apremilast; BID = twice daily; PASI = Psoriasis Area and Severity Index.
Note: Subjects were censored after the addition of topical/photo or other effective psoriasis therapies.
Source: PSOR-009 CSR Figure 14.

Response Outcomes in Study PSOR-008

Of the subjects who lost their PASI-75 response, the magnitude of loss was greater for those on placebo compared with those on APR 30 mg BID. Of the subjects who lost their PASI-75 response while remaining on APR 30 mg BID treatment, almost 60% were just below PASI-75 (PASI 70 to 74) when response was lost, and 90% were still above PASI-60. Of the 63 subjects who were re randomized to placebo and lost their PASI-75 response, approximately 30% were just below PASI-75 (PASI 70 to 74) when the response was lost, and approximately 70% were above PASI-60.

Response Outcomes in Study PSOR-009

Fewer subjects (11.5%) re-randomized to APR 30 BID lost 50% of the PASI improvement obtained at Week 32 compared with those re randomized to placebo (56.5%). Of the subjects who lost response, the magnitude of loss was greater for those on placebo compared with those on APR 30 BID. Of the 7 subjects who lost response while remaining on APR 30 mg BID treatment, 57.1% (4/7) were below PASI-30 at the time of loss of response.

Of the 35 subjects who were re-randomized to placebo and lost their response, 62.9% (22/35) were below PASI-30 when the response was lost. A total of 61 subjects with a PASI-50 response at Week 32 were re-randomized to continue receiving APR 30 BID through Week 52, of whom, 36 subjects (59.0%) were PASI-75 responders and 25 (41.0%) were PASI 50 to 74 responders. At Week 52, 30 of the 61 subjects (49.2%) were PASI-75 responders and 19 (31.1%) were PASI 50 to 74 responders.

Among subjects who had been PASI-75 responders at Week 32, 31 were re-randomized to placebo and 36 were re-randomized to APR 30 BID. Of the re-randomized subjects, 28/31 (90.3%) in the APR 30 BID/APR 30 BID/placebo and 17/36 (47.2%) in the APR 30 BID/APR 30 BID/APR 30 BID treatment groups lost their PASI-75 response in the Randomized Withdrawal Treatment Phase.

For the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, median time to first loss of PASI-75 was 4.3 weeks and 20.9 weeks from the Week 32 re randomization, respectively (nominal $p < 0.0001$).

Retreatment Following Relapse in Study PSOR-008

Once subjects re-randomized to placebo demonstrated a loss of PASI-75 response, they resumed treatment with APR 30 BID. This resumption of treatment with APR 30 BID occurred no later than Week 52.

A total of 64 of the 77 subjects re-randomized to placebo resumed treatment with APR 30 BID following loss of PASI-75 response prior to Week 52. These 64 subjects were retreated with APR 30 BID for a mean duration of 13.8 weeks.

Of these 64 retreated subjects, 70.3% achieved PASI-75 after retreatment during Weeks 32 to 52, with 51.6% of subjects regaining PASI-75 response within 4 weeks after retreatment.

Retreatment Following Relapse in Study PSOR-009

For subjects originally randomized to APR 30 mg BID at baseline (Week 0), PASI-50 responders were randomly assigned 1:1 to maintain dosing on APR 30 mg BID or to placebo (treatment withdrawal) at Week 32. Once subjects lost 50% improvement in PASI score obtained at Week 32 compared to baseline, they resumed treatment with APR 30 mg BID. This resumption of treatment with APR 30 BID occurred after Week 32 and prior to Week 52.

A total of 32 subjects re-randomized to placebo lost 50% of the PASI improvement at Week 32 compared to baseline and resumed treatment with APR 30 mg BID during the Randomized Treatment Withdrawal Phase. These 32 subjects were retreated with APR 30 BID for a mean duration of 11.4 weeks. Of these 32 retreated subjects, 65.6% achieved PASI-50 after retreatment at some time point, with 34.4%, 51.7%, and 53.3% of subjects achieving PASI-50 after 4, 8, and 16 weeks of retreatment, respectively.

Static Physician Global Assessment

Of the subjects rerandomized to APR 30 mg BID, 75.3% of the subjects in Study PSOR-008 and 41.0% of subjects in Study PSOR-009 had an sPGA score of 0 or 1 (clear or almost clear) at Week 32. At Week 52, 51.9% of the subjects in Study PSOR-008 and 36.1% of subjects in Study PSOR-009 had an sPGA score of 0 or 1 (clear or almost clear).

Body Surface Area Involvement

In Study PSOR-008, all treatment groups (APR 30 BID/APR 30 BID/APR 30 BID, APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/placebo/APR 30 BID) had similar mean percent decreases in BSA involvement from baseline (≥ 80%) at Week 52.

In contrast, in Study PSOR-009, the mean percent decrease in BSA involvement from baseline was approximately 80% for those subjects re-randomized to APR 30 mg BID but was approximately 64% to 66% for those subjects re-randomized to placebo. The differences observed between treatment groups may be reflective of the protocol-specified population for re-randomization as well as definitions for loss of response. In Study PSOR-008, re-randomized subjects were those who were PASI-75 responders at Week 32, whereas in Study PSOR-009 it was the PASI-50 responders at Week 32 who were re randomized.

Dermatology Life Quality Index

Subjects re-randomized to APR 30 mg BID experienced clinically meaningful improvements (mean and median decreases) in DLQI Total Score from baseline of at least -7.5 at Week 52 in both studies. In Study PSOR-008, 77% of subjects re randomized to APR 30 mg BID at Week 32 had clinically meaningful improvement in DLQI (≥5-point decrease in DLQI; and composite endpoint of ≥5-point decrease in DLQI and PASI-50 response) at Week 52. In Study PSOR-009, 70.0% had a ≥5-point decrease in DLQI Total Score from baseline, and 62.0% achieved the composite endpoint of ≥5-point decrease in DLQI Total Score from baseline and a PASI-50 response at Week 52.

Visual Analog Scales

During the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) in both studies, subjects who remained on APR 30 mg BID therapy (APR 30 BID/APR 30 BID/APR 30 BID) generally maintained improvements in VAS-related endpoints.

In both studies, the subjects re-randomized to apremilast (APR 30 BID/APR 30 BID/APR 30 BID) generally maintained improvements in Skin Discomfort/Pain VAS (>30 mm decrease from baseline) at Week 52.

Health-related Quality of Life

In general, improvements in health-related quality of life assessments were sustained by subjects in all treatment groups during the Randomized Treatment Withdrawal Phase (Weeks 32 to 52). Subjects re-randomized to APR 30 mg BID at Week 32 (APR 30 BID/APR 30 BID/APR 30 BID) achieved a mean change (improvement) from baseline in SF-36v2 MCS of 3.87 in Study PSOR-008 and 3.20 in Study PSOR-009 at Week 52; both exceeded the MCID of 2.5.

In both studies, subjects re-randomized to placebo (APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/placebo/APR 30 BID) also achieved improvements in SF-36v2 MCS that exceeded the MCID of 2.5 at Week 52.

Subjects re-randomized to APR 30 mg BID at Week 32 achieved mean change (improvements) from baseline in SF-36v2 PCS of 1.3 in Study PSOR-008 and 2.65 in Study PSOR-009 at Week 52.

For subjects re randomized to placebo at Week 32 in both studies, mean change (improvement) from baseline at Week 52 was greater for subjects who remained on placebo treatment up to Week 52 (APR 30 BID/APR 30 BID/placebo) than for those subjects who resumed APR 30 BID treatment prior to Week 52 (APR 30 BID/APR 30 BID/placebo/APR 30 BID).

Subjects re randomized to APR 30 BID at Week 32 achieved mean change (improvements) from baseline in PHQ-8 of -0.7 in Study PSOR-008 and -1.0 in Study PSOR-009 at Week 52. For subjects re randomized to placebo at Week 32 in Study PSOR-008, mean change (improvement) from baseline at Week 52 was greater for subjects who remained on placebo treatment up to Week 52 (APR 30 BID/APR 30 BID/placebo) than for those subjects who resumed APR 30 BID treatment prior to Week 52 (APR 30 BID/APR 30 BID/placebo/APR 30 BID).

In Study PSOR-009, the mean changes (improvements) were similar between subjects who remained on placebo treatment up to Week 52 (APR 30 BID/APR 30 BID/placebo) and for subjects who resumed APR 30 BID treatment prior to Week 52 (APR 30 BID/APR 30 BID/placebo/APR 30 BID).

Nail Assessments

All nail parameters indicate sustained improvement in subjects treated with APR 30 BID from baseline through Week 52. In both studies, subjects rerandomized to APR 30 mg BID at Week 32 had a mean change in NAPSI score from baseline of approximately -60% at Week 52. The mean number of involved nails in this treatment group decreased by 3.3 and 2.7 in Studies PSOR-008 and PSOR-009, respectively, ie, these nails were cleared of psoriasis. Approximately 63% of subjects re-randomized to APR 30 BID at Week 32 in both studies achieved NAPSI-50 at Week 52.

Scalp Psoriasis

In Studies PSOR-008 and PSOR-009, among subjects with moderate or more severe scalp psoriasis at baseline who rerandomized to APR 30 BID at Week 32, over 72% and 54%, respectively, achieved ScPGA scores of 0 or 1 (clear or minimal) at Week 52 and 77.1% and 62.2%, respectively, achieved ScPGA scores of 0, 1, or 2 (clear, minimal, or mild) at Week 52.

In Study PSOR-008, among subjects with moderate or more severe scalp psoriasis at baseline who rerandomized to placebo and resumed APR 30 mg BID, approximately 52% of subjects had an ScPGA score of 0 or 1 (clear or minimal) at Week 52 and 67.4% had an ScPGA score of 0, 1, or 2 (clear, minimal, or mild) at Week 52. In Study PSOR-009, among subjects with moderate or more severe scalp psoriasis at baseline who rerandomized to placebo and resumed APR 30 BID, 17.5% of subjects had an ScPGA score of 0 or 1 at Week 52 and 27.5% had an ScPGA score of 0, 1, or 2 (clear, minimal, or mild) at Week 52.

Palmoplantar Psoriasis

In Studies PSOR-008 and PSOR-009, among subjects with a moderate or severe palmoplantar psoriasis at baseline who rerandomized to APR 30 mg BID, 87.5% and 100%, respectively, achieved PPPGA scores of 0 or 1 (clear or almost clear) at Week 52 and 87.5% and 100%, respectively, achieved PPPGA scores of 0, 1, or 2 (clear, almost clear, or mild) at Week 52.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Psoriatic arthritis

The MAH has undertaken four multicenter, randomized, double-blind, placebo-controlled Phase 3 clinical studies (PSA002, PSA003,PSA004 PSA-005) and one additional phase 2 study in support of this application in patients with active arthritis. None of these studies were conducted with an active comparator. While this complies with the CHMP guidance and scientific advice, the CHMP considered that it would have been helpful if an active controlled arm had been included. The applicant has provided a comparison of the efficacy and safety with historical data for a range of small molecule and large molecule DMARDs which gives some indication as to how apremilast might compare with other active treatments. The studies did not include endpoints to show the impact of apremilast on progression of structural changes however although no radiographic evidence is available in patients with psoriatic arthritis, the available nonclinical and clinical data (in patients with RA) do not indicate that any unexpected, deleterious effects or MRI evidence of inhibition of structural damage on cartilage, bone, or joints occur

following treatment with apremilast. Consideration should be given to inclusion of radiographic endpoints in future studies with apremilast in PsA. The data after stopping therapy (i.e. a randomised withdrawal phase) have not been evaluated in this program. The CHMP considered that this would have been useful in terms of evaluating the effect of withdrawal of treatment on persistence of effect or the possibility treatment holidays.

The current study design supports second or third line treatment in patients who have previously failed treatment or have had an inadequate response with small molecule and biological DMARDS. Initially the applicant proposed an indication for use also in patients who have a contraindication to a DMARD therapy. The CHMP considered that contraindication to DMARD therapy was not included as a specific inclusion criterion and patients were not stratified a priori according to this criterion. To support the proposed indication in the 'contraindication' subgroup the applicant has identified a subgroup of subjects with a 'contraindication' to a DMARD therapy who have been included in the pivotal apremilast studies PSA-003 and PSA-004. The applicant also refered to the experience gained in DMARD-naïve ("first line") patients treated with apremilast in the supportive Phase 3 study PSA-005 and argued that as MTX confers little clinical benefit in patients with active PsA (Kingsley, 2012) they did not employ MTX as an active comparator in this study. The recommendations of international scientific societies, such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) (Ritchlin2009) or the European League Against Rheumatism (EULAR) (Gossec2012) propose MTX as a potential first-line DMARD therapy in the management of psoriatic arthritis but acknowledge the limited evidence base for this recommendation. This strengthens the need for head to head comparator studies with established treatments such as MTX and newer agents using standardised criteria outlined in regulatory guidance. The CHMP therefore considered that data with an established active comparator for first line treatment of psoriatic arthritis patients who are not controlled by NSAIDs is needed. The clinical relevance of this poorly defined 'contraindication 'subgroup is questionable and the CHMP concluded that the inclusion in section 4.1 of an indication for use in patients with a contraindication to DMARD therapy was not supported. This was agreed by the MAH and the product information has been udapted accordingly.

The apremilast indication therefore reads as follows:

"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".

The numbers across dose groups receiving physical therapy was considered small (<1%) by CHMP and may reflect the lack of access to appropriate multidisciplinary care. However the CHMP agreed that there was no impact on the overall clinical outcomes of the PsA pivotal studies.

Plaque psoriasis

The pivotal Phase 3 studies of apremilast for monotherapy use in psoriasis (Studies PSOR-008 and PSOR-009) utilised a similar study design. Both studies consisted of 4 treatment phases: a 16-week, randomized, double-blind, placebo-controlled phase; a 16-week double-blind maintenance phase; a 20-week randomized, double-blind treatment withdrawal phase; and a 208-week, open-label long-term safety extension phase. Overall study duration was 5 years.

The applicant enrolled a range of patients treatment naive (to all systemic or phototherapy) and patients whom were treatment experienced and had failed a number of treatments. The demographic characteristics of subjects, disease history, prior use of psoriasis related therapies and disease activity at baseline were similar across studies and were generally well balanced across treatment groups.

In Study PSOR-008 at Week 32 (Randomized Treatment Withdrawal Phase), subjects originally randomized to APR 30 BID at baseline who had achieved a 75% reduction in the PASI score [PASI-75] were re-randomized to either APR 30 BID or placebo to evaluate time to loss of PASI-75 response. Subjects who were re-randomized to placebo and lost their PASI-75 response restarted APR 30 BID without retitration. In contrast, Study PSOR-009 utilized a different definition of responder and loss of effect in the Randomized Treatment Withdrawal Phase. In this study at Week 32 (Randomized Treatment Withdrawal Phase), subjects originally randomized to APR 30 BID at baseline who had achieved a PASI-50 response were re-randomized to either APR 30 BID or placebo to evaluate time to loss of 50% of the PASI improvement at Week 32 compared to baseline. Subjects who were re-randomized to placebo and lost 50% of their PASI response at Week 32 restarted APR 30 BID without retitration.

In the scientific advice provided to the applicant, the CHMP stated that PASI 75 alone was not sufficient as a single endpoint and advised to also power for IGA 0-1. Also the CHMP recommended conducting a three arm study with an active comparator with a preference to use methotrexate as an active comparator. The applicant is currently conducting a comparator trial with etanercept (Study CC-10004-PSOR-010 is phase 3b study, double-blind, double-dummy, 3-arm study comparing apremilast and etanercept versus placebo in subjects with moderate to severe plaque psoriasis). The applicant will provide the full study report when finalised (as described in the RMP). At the present time, a justification that the efficacy and safety data support a broad indication in patients in need of systemic therapy was considered inadequate, in particular since an active comparator study with a conventional systemic therapy has not been presented for assessment. It is therefore difficult at the present time to put the efficacy and safety of this product into context with other systemic therapies. Notwithstanding this, the benefit/risk remains positive for marketing authorisation. The applicant also agreed to amend the indication to a second line population: “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)”. This was agreed by the CHMP.

Efficacy data and additional analyses

Psoriatic arthritis

The key primary endpoint (ACR 20 response rate) was met to a statistical level across the three pivotal studies (FAS). This is supported by a range of sensitivity analyses. In the pooled analysis, 32% in the APR 20 BID treatment group and from 37% in the APR 30 BID treatment group achieved the mACR primary endpoint at week 16. In the pooled analysis a treatment effect compared with placebo in favour of apremilast 30 BID (mACR primary endpoint 13.2% and 18.3% at week 16 and 13% and 15.8% at week 24 ($p<0.0001$)) was demonstrated for APR20 BID and APR30 BID groups respectively. The duration of effect after the primary endpoint of 16 weeks was evaluated in a placebo controlled manner at week 24. From the available data at week 24 (FAS NRI) and from week 24-50 (APR analyses using OC and NRI) a treatment effect in favour of apremilast is apparent from 16 to 24 weeks and is maintained up to 52 weeks. At Week 52 across the three pivotal studies in patients initially randomised to APR (NRI), the modified ACR 20 response rates observed in the APR 20 BID and APR 30 BID treatment groups were generally comparable (Pooled analysis APR20 BID 40.8%; APR30BD 42.1%). This data suggests that efficacy is maintained through week 52.

In terms of a dose effect, the modified ACR 20 response rates observed in the pooled data for APR 20 BID and APR 30 BID treatment showed a treatment effect in favour of APR30 BID at week 16. During the 24-52 week treatment period efficacy levels are generally maintained. The applicant proposed a standard starting dose of 10 mg titrated up to 30 mg over one week. Although the Phase III data does not clearly distinguish between the 20 mg BID and 30 mg BID dose, overall the weight of evidence from the primary

and secondary endpoints is in favour of the 30 mg BID dose as the proposed treatment dose. This was agreed by the CHMP.

Current CHMP guidelines recommend that axial involvement should be assessed as an important secondary endpoint. BASDAI was evaluated as an exploratory analysis. The study population enrolled in the apremilast PsA Phase 3 program included subjects with the following clinical subtypes of PsA: symmetric polyarthritis (62.0%), asymmetric oligoarthritis (26.9%), distal interphalangeal (DIP) joint predominant (6.2%), arthritis mutilans (2.7%) and spondylitis predominant (2.1%). Axial involvement, a common secondary feature of peripheral predominant PsA disease, was present in 37% (548/1493) of subjects enrolled in the Phase 3 program. A further review of efficacy data in the subpopulation of PSA patients who have axial involvement secondary to peripheral join involvement was provided by the applicant. The prevalence of axial involvement reported in the literature varies due to the lack of an accepted definition of spinal involvement in axial arthritis PsA. According to several reports, spinal involvement in patients with PsA ranges from 25% to 70% of cases. The relative proportion of axial involvement in the apremilast phase 3 study population falls within this range (37% (548/1493) of subjects enrolled in the Phase 3 program). The efficacy of apremilast 30 mg twice daily has been demonstrated in the sub-population of subjects with axial disease Baseline BASDAI Score $\geqslant$4 (pooled data at week 16 and 24 mean difference with placebo -0.57 p=0.0173 and -0.85 p=0.007 respectively), thereby supporting some level of efficacy in this subgroup with axial involvement as a secondary feature of peripheral predominant PsA disease. In the predominant spondylitis subgroup 3/12 (25%) of APR30mg BID vs 2/7 (28.6%) placebo had a treatment effect in favour of placebo. The numbers of subjects with predominant spondylitis make it difficult to draw meaningful conclusions from these data. The CHMP considered that it is unnecessary to restrict the indication by specifically excluding patients with axial disease as this could result in patients who could benefit from treatment being denied treatment. Clinically relevant information from subgroup or post-hoc analyses in patients with predominately spondylitic disease and in patients with axial involvement as a secondary feature of peripheral predominant PsA disease, reflecting the limited robustness of these observations is included in the product information as requested by the CHMP.

Mean change in HAQ-DI from baseline in the APR 30 BID treatment group in all three studies at Weeks 16 was -0.2. The treatment effect in terms of difference with placebo was -0.14 in APR30mg BID pooled analysis. This mean change from baseline for APR30 BID achieved statistical significance with placebo at week 16 and 24. The minimal clinically important difference (MCID) in HAQ-DI reflecting a meaningful improvement in physical function has not been clearly described for patients with PsA. However minimum clinically important difference (MCID) values were identified in the published literature available at the time of the protocol development and study conduct (change from baseline of -0.3[Mease, 2004a] and -0.35 [Mease 2011b] and a further estimate, change from baseline of -0.13 [Kwok, 2010]). When group median (and mean) changes well exceed the MCID, it can be expected that a majority of patients will attain clinically meaningful improvement. The mean improvements from baseline (pooled analysis) exceeded a MCID ≥ 0.13 however did not exceed a MCID of >0.3.At week 16, a range of 33.5% to 38% in the APR30mg BID group across all three studies had achieved ≥0.3-unit improvement in the HAQ-DI. The treatment effect in terms of difference with placebo ranged from 5.1% to 5.9% in the APR 20mg BID group and 6.9% to 13.2% in APR30mg BID across the three studies (nom.sig in studies PSA-002 and PSA003 for 30mg BID group).

The CHMP concluded that apremilast has been shown to improve physical function. The MCID for HAQ-DI in psoriatic arthritis has not been clearly established. The statement: “Otezla has been shown to improve physical function” has therefore been removed from the indication by the applicant.

Plaque psoriasis

The primary endpoint of both studies was the proportion of subjects treated with either APR 30 BID or placebo who achieved a PASI-75 response at Week 16 compared to baseline. In both studies, a statistically significantly greater proportion of subjects in the APR 30 BID treatment group achieved the primary endpoint, compared with placebo ($p < 0.0001$ for both studies), as evaluated using the primary analysis method (i.e. missing values at Week 16 imputed using LOCF). The results for the primary endpoint (PASI 75) and key secondary endpoint (sPGA) were supported by the sensitivity analyses conducted to assess the impact of missing data. All these sensitivity analyses demonstrated similar results and statistically significant differences between the APR 30 BID treatment group compared with placebo treatment group ($p < 0.0001$ for all sensitivity analyses).

The major secondary endpoint was the proportion of subjects treated with either APR 30 BID or placebo with an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16 (Feldman, 2005). The applicant also examined additional endpoints such as Scalp Physician Global Assessment (ScPGA), Dermatology Life Quality Index (DLQI), Patient Health Questionnaire depression scale (PHQ-8), Nail Psoriasis Severity Index (NAPSI), Palmoplantar Psoriasis Physician Global Assessment (PPPGA) and Short Form 36-item Health Survey ect.

In both studies, a statistically significantly greater proportion of subjects in the APR 30 BID treatment group achieved sPGA score of 0 (clear) or 1 (almost clear), with at least a 2-point reduction from baseline at Week 16 compared with placebo ($p < 0.0001$). The response rates in the placebo and APR 30 BID treatment groups were 3.9% and 21.7%, respectively, in Study PSOR-008, and were 4.4% and 20.4%, respectively, in Study PSOR-009.

The composite endpoint was defined as the number of subjects who achieved both a PASI-75 and sPGA scores of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16. In both pivotal studies, a nominally significantly greater proportion of subjects in the APR 30 BID treatment group achieved the composite endpoint at Week 16 compared with placebo (nominal $p < 0.0001$). Similar findings were observed in the PP population. PSOR 008 and PSOR 009 showed a 16.7 % and 14.2% greater response rate response in favour of APR 30 MG BID at 16 weeks.

The mean DLQI Total Scores at baseline were approximately 12.5 in both pivotal studies, indicating a significant impact of psoriasis on the subjects' quality of life. In both studies, subjects treated with APR 30 BID achieved statistically significant improvement (reduction) in the DLQI Total Score at Week 16 compared with placebo ($p < 0.0001$).

The mean changes from baseline were -2.1 and -6.6 for subjects treated with placebo or APR 30 BID, respectively, in Study PSOR-008 and were -2.8 and -6.7, respectively, in Study PSOR-009. The mean improvement at Week 16 for the APR 30 BID treatment group of 6.6 in Study PSOR-008, and 6.7 in Study PSOR-009, exceeded the Minimal Clinically Important Difference (MCID) of at least a 5-point decrease from baseline (Finlay, 1994; NICE, 2012).

Overall, 558 of the 844 subjects (66%) enrolled in Study PSOR-008 and 266 of the 411 subjects (64.7%) enrolled in Study PSOR-009 had nail psoriasis at baseline. The percent mean change from baseline at Week 16 for placebo-treated subjects was 6.5% and -7.1% in Studies PSOR-008 and PSOR-009, respectively, and for apremilast-treated subjects was -22.5% and -29.0% in Studies PSOR-008 and PSOR-009, respectively. Although a positive response to treatment is seen, it is not known why the placebo groups appear to opposite to each other in the two studies.

The proportion of subjects with an ScPGA score of 0 or 1 (clear or minimal) were 17.5% and 46.5% for placebo and APR 30 BID treatment groups, respectively, in Study PSOR-008 and were 17.2% and 40.9%, respectively in Study PSOR-009, both results were statistically significant better in favour of treatment.

For both studies, the PASI-75 response rates for subjects originally randomised to APR 30 BID were generally maintained through Week 32. Subjects originally randomized to placebo demonstrated a response to apremilast treatment, similar to that seen for subjects originally randomized to APR 30 BID at baseline. By Week 24, the PASI response rates for subjects who were originally randomized to placebo following 8 weeks of APR 30 BID treatment were generally comparable to those for subjects receiving 24 weeks of APR 30 BID.

The sPGA response rates for subjects originally randomized to APR 30 BID peaked around Week 16 in both studies and were generally maintained through Week 32. Subjects originally randomized to placebo demonstrated rapid sPGA response following initiation of apremilast treatment, similar to that seen for subjects originally randomized to APR 30 BID at baseline. By Week 24, the response rates for subjects originally randomized to placebo following 8 weeks of APR 30 BID treatment were similar to those for subjects who received 24 weeks of APR 30 BID.

At Week 32, after placebo subjects had been treated with APR 30 BID for 16 weeks, reductions in BSA involvement were similar between the treatment groups, and greater than the changes at Week 16. The mean percent changes (improvement) from baseline in BSA involvement for the placebo/APR 30 BID and APR 30 BID/APR 30 BID treatment groups were -59.25% and -61.18%, respectively, in Study PSOR-008 and -58.73% and -60.67%, respectively, in Study PSOR-009.

At Weeks 24 and 32 in both studies, subjects originally randomized to placebo achieved similar changes in DLQI Total Scores from baseline as did those subjects originally randomized to APR 30 BID and were greater than the changes observed at Week 16. Patients continuing treatment on APR 30 mg BID had similar change form baseline responses at 24 and 32 weeks and similarity in DLQI changes were seen between both studies. However in the proportion of patients with at least a 5 point change in DLQI is slightly lower for patients continuing on treatment at 24 weeks versus 32 weeks.

The longer duration of treatment with APR 30mg BID was associated with better NASPSI score, however the difference seen in NAPSI score change for patients initially on placebo and then switched to APR 30mg bid is different between the two studies (PSOR 008 at week 32 mean -24.6 compared with -47.6 in OO9 study- although it is recognised there is large variability). Approximately half of patients enrolled also had scalp psoriasis, of the subjects with ScPGA score ≥3 (moderate or greater) at baseline, the proportion of subjects who achieved an improvement of ScPGA score of 0 or 1 (clear or minimal) was numerically greater for the placebo/APR 30 BID group than for the APR 30 BID/APR 30 BID group at Weeks 24 and 32. Again in patients maintaining therapy throughout there appears to be a lower effect at 32 weeks compared with 24 weeks treatment, and about 10 % higher in patients who were initially treated with placebo.

Palmoplantar Psoriasis Analyses During the Maintenance Phase (Weeks 16 to 32) in Studies PSOR-008 and PSOR-009 (FAS With Baseline PPPGA ≥3) the patient numbers are too low to draw any meaningful conclusions on palmoplantar psoriasis, however improvement is seen with treatment versus placebo and it appears to be maintained over time.

Subjects who were re-randomized were those subjects originally randomized to APR 30 BID and achieved a PASI-75 response (Study PSOR-008) or at least a PASI-50 response (Study PSOR-009) at Week 32, were re-randomized to either APR 30 BID or placebo in order to evaluate time to first loss of effect.

Of the re-randomized subjects in PSOR 008 the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment group, 63/77 subjects (81.8%) and 40/77 subjects (51.9%), respectively, lost PASI-75 response at some time point during the Randomized Treatment Withdrawal Phase. The median time to first loss of PASI-75 was 5.1 weeks and 17.7 weeks from the Week 32 re-randomization, respectively (nominal p <0.0001).

In contrast to PSOR-008, the time to first loss of effect in Study PSOR-009 was defined as loss of 50% of the improvement in PASI score obtained at Week 32 compared to baseline after re randomization in the Randomized Treatment Withdrawal Phase.

For the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively, 35/62 subjects (56.5%) and 7/61 subjects (11.5%) lost 50% of their Week 32 PASI improvement at some time point during the Randomized Treatment Withdrawal Phase.

The median time to a loss of 50% of the improvement in PASI score obtained at Week 32 compared to baseline was 12.4 and 21.9 weeks following the Week 32 re-randomization for the APR 30 BID/APR 30 BID/placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively (nominal p <0.0001).

While patients randomised to continued treatment have a longer duration of response and a higher percentage of patients maintaining either PASI 75 or PASI 50, a considerable number of patients lose PASI 75 with continued treatment (PSOR 008 – 51.9%) although the patient numbers are low and 57.5% have PASI scores of 70-74, it is unclear why this occurs. However longer term efficacy data is awaited from the ongoing studies 008 and 009 (as described in the RMP).

Of the subjects re-randomized to APR 30 BID, 75.3% of the subjects in Study PSOR-008 and 41.0% of subjects in Study PSOR-009 had an sPGA score of 0 or 1 (clear or almost clear) at Week 32. At Week 52, 51.9% of the subjects in Study PSOR-008 and 36.1% of subjects in Study PSOR-009 had an sPGA score of 0 or 1 (clear or almost clear). Both studies also showed that patients continuing on treatment had a longer time to loss of s PGA approximately 20 weeks compared with placebo 4-5 weeks. Similar to the PASI loss with continued treatment approximately 40% of patient on continued treatment fail to maintain s PGA of 0-1 32 weeks to 52 weeks.

Subjects re-randomized to APR 30 BID experienced clinically meaningful improvements (mean and median decreases) in DLQI Total Score from baseline of at least -7.5 at Week 52 in both studies. In Study PSOR-008, 77% of subjects re-randomized to APR 30 BID at Week 32 had clinically meaningful improvement in DLQI (≥ 5-point decrease in DLQI; and composite endpoint of ≥ 5-point decrease in DLQI and PASI-50 response) at Week 52. In Study PSOR-009, 70.0% had a ≥5-point decrease in DLQI Total Score from baseline, and 62.0% achieved the composite endpoint of ≥5-point decrease in DLQI Total Score from baseline and a PASI-50 response at Week 52. Patients whom were randomised to placebo at 32 weeks and were re-treated with APR 30 mg BID generally had the same scores as patients continuing on treatment until 52 weeks, however similar to the PASI and sPGA scores it appears that patients on active treatment have better results at 32 weeks compared with 52 weeks. Longer term efficacy data is awaited from the ongoing studies 008 and 009 (as described in the RMP).

All nail parameters indicate sustained improvement in subjects treated with APR 30 BID from baseline through Week 52. In both studies, subjects re-randomized to APR 30 BID at Week 32 had a mean change in NAPSI score from baseline of approximately -60% at Week 52. The mean number of involved nails in this treatment group decreased by 3.3 and 2.7 in Studies PSOR-008 and PSOR-009, respectively, i.e., these nails were cleared of psoriasis. Approximately 63% of subjects rerandomized to APR 30 BID at Week 32 in both studies achieved NAPSI-50 at Week 52.

In Studies PSOR-008 and PSOR-009, among subjects with moderate or more severe scalp psoriasis at baseline who rerandomized to APR 30 BID at Week 32, over 72% and 54%, respectively, achieved ScPGA scores of 0 or 1 (clear or minimal) at Week 52 and 77.1% and 62.2%, respectively, achieved ScPGA scores of 0, 1, or 2 (clear, minimal, or mild) at Week 52. Patients on APR 30 mg BID whether continuous or retreated have better ScPGA scores than patients on placebo at 52 weeks, patients on continuous treatment have better results compared with patients who are retreated following randomisation to

placebo. Although patient numbers are low the ScPGA scores of 0-1 are higher at week 32 compared with week 52 for patients continuing on treatment.

In Studies PSOR-008 and PSOR-009, among subjects with a moderate or severe palmoplantar psoriasis at baseline who rerandomized to APR 30 BID, 87.5% and 100%, respectively, achieved PPPGA scores of 0 or 1 (clear or almost clear) at Week 52 and 87.5% and 100%, respectively, achieved PPPGA scores of 0, 1, or 2 (clear, almost clear, or mild) at Week 52. The studies showed efficacy in patients with palmoplantar psoriasis with continued treatment to 52 weeks, however patient numbers are too low to draw meaningful conclusions.

2.5.4. Conclusions on the clinical efficacy

Psoriatic Arthritis

A treatment effect in favour of apremilast (mACR primary endpoint 18.3% at week 16 and 15.8% at week 24 $p<0.0001$) was demonstrated for APR30mg BID across the three studies in patients who have previously failed or have not responded to prior DMARD therapy in terms of treatment of symptoms and clinical indices of articular disease activity both for those on DMARDs (small molecule and biological) and for those not on DMARDs at baseline.

Improvement in the signs and symptoms of PsA, as measured by the modified ACR 20 response at week 16, continued up to Week 52 across all three pivotal Phase 3 studies.

Improvement in physical function was evaluated using HAQ-DI score, SF-36v2 physical functioning domain score statistically and nominally significant improvements were seen across both these endpoints across all three studies at week 16 and were maintained across week 24 and 52. Improvement in physical function evaluated using HAQ-DI was supported by a change from baseline in the average HAQ-DI score of -0.2 across all three studies for APR30mg BID The HAQ-DI score was also maintained between Week 24 and Week 52.

The results of the ACR20 analysis were supported by the results of the modified PsARC, DAS28[CRP], EULAR good/moderate response) analyses. A positive treatment effect was also observed irrespective of the number or type of prior small-molecule DMARD or biologic used.

A consistent, improvement in modified ACR 20 responses, compared to placebo, was observed irrespective of whether apremilast was given alone (approximately 35% of subjects) or in combination with concomitant small-molecule DMARDs (approximately 65% of subjects).

Improvements in extra articular manifestations of psoriatic disease (PASI-75, MASES, dactylitis severity score), and health-related quality of life (SF-36v2 PCS score, FACIT-Fatigue score) at Weeks 16 and 24, and these improvements were broadly maintained at Week 52 with continued apremilast treatment.

There was no formal comparison of efficacy between the APR 20 BID and APR 30 BID treatment groups but in general higher and more consistent responses were observed for subjects receiving APR 30 BID over APR 20 BID up to week 24 (the placebo –controlled period).

The CHMP concluded that the inclusion in section 4.1 of an indication for use in patients with a contraindication to DMARD therapy was not supported. This was agreed by the MAH and the product information has been udapted. The apremilast indication therefore reads as follows:

“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”.

The CHMP also concluded that apremilast has been shown to improve physical function. The MCID for HAQ-DI in psoriatic arthritis has not been clearly established. The statement: “Otezla has been shown to improve physical function” has therefore been removed from the indication by the applicant.

Plaque psoriasis

Efficacy has been demonstrated for patients with plaque psoriasis for induction at 16 weeks and short maintenance for an additional 16 weeks. Pooled analysis shows a statistical significant difference in favour of Apremilast 30mg bid for PASI 75 at 16 weeks (26.2 % improvement) and s PGA (17.2 % improvement) versus placebo, and 15.9% of patients achieving both PASI 75 and sPGA 0-1 at 16 weeks, with higher efficacy observed at later time points.

Continued treatment shows maintenance of effect of PASI and sPGA in weeks 16 to 32, and patients continued on treatment having significantly longer time before loss of PASI 75, PASI 50 or s PGA is observed at week 32 to 52.

Also patients who were treated with placebo in the randomised withdrawal phase showed significant responses following retreatment with Apremilast 30mg BID.

As an active comparator study with a conventional systemic therapy such as methotrexate was not conducted, it is difficult to rank this product with other first line systemic conventional therapies. An active comparator study versus etanercept is being conducted in patients failing conventional systemic therapy. The applicant will provide the full study report when finalised (as described in the RMP). At the present time, a justification that the efficacy and safety data support a broad indication in patients in need of systemic therapy was considered inadequate, in particular since an active comparator study with a conventional systemic therapy has not been presented for assessment. It is therefore difficult at the present time to put the efficacy and safety of this product into context with other systemic therapies. Notwithstanding this, the benefit/risk remains positive for marketing authorisation. The applicant therefore agreed to amend the indication to a second line population: “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)”.

2.6. Clinical safety

Introduction

The overall safety evaluation plan assessed the safety data obtained from a total of 30 clinical studies of apremilast, including 16 clinical pharmacology studies and 14 Phase 2/ 3 studies in various indications. Of the 16 clinical pharmacology studies conducted with apremilast, 13 were in healthy subjects (N=422) and 3 were in non healthy subjects (N=39). The non healthy subjects comprised 15 subjects with PsA or RA, 8 subjects with severe renal impairment, and 16 subjects with hepatic impairment. The 14 Phase 2/ 3 studies included primary and supporting clinical studies as follows: 6 in psoriasis, 5 in PsA, 1 in RA, 1 in Behçet’s disease, and 1 in asthma. In these studies, the following apremilast dosage regimens were evaluated: 10 mg twice daily (APR 10 BID), 20 mg once daily (APR 20 QD), 20 mg BID (APR 20 BID), 40 mg QD (APR 40 QD), and 30 mg BID (APR 30 BID). The Phase 2/3 studies in PsA and psoriasis (except PSOR-001, PSOR-004) had a placebo controlled treatment phase. Studies PSOR-005-E-LTE, PSOR-008, PSOR-009, PSA-002, PSA-003, PSA-004, and PSA-005 also have open-label, active-treatment, long-term extension phases. The planned duration of the placebo-controlled phases in these studies ranged from 12 to 24 weeks.

Patient exposure

Apremilast Data Pool

A summary of total exposure to apremilast in the Apremilast Data Pool, which includes subjects initially randomized to apremilast as well as placebo subjects who switched to apremilast, is presented in Table 59. A total of 4089 subjects received at least one dose of apremilast. In the Apremilast Data Pool, 3049 (74.6%) subjects received apremilast (APR Total groups) for at least 24 weeks, including 1024 (70.6%) subjects who received APR 20 BID and 1930 (81.9%) subjects who received APR 30 BID. A total of 1631 (39.9%) subjects had been exposed to apremilast (APR Total group) for at least 52 weeks in completed and ongoing studies, including 510 (35.2%) subjects in the APR 20 BID group and 1107 (47.0%) subjects in the APR 30 BID group, as of the cut-off dates for the submission, i.e., 01 Mar 2013 for ongoing PsA studies (Studies PSA-002, PSA-003, PSA-004, PSA-005) and 11 Jan 2013 for ongoing psoriasis studies (PSOR-008, PSOR-009, and PSOR-005-E-LTE).

Table 59: Apremilast Data Pool: Extent of Apremilast Exposure (Apremilast Subjects as Treated)

	APR 20 BID (N=1450) n (%)	APR 30 BID (N=2357) n (%)	APR Total[a] (N=4089) n (%)
Exposure Category[b]			
≥ 1 Day	1450 (100)	2357 (100)	4089 (100)
≥ 4 Weeks	1396 (96.3)	2259 (95.8)	3924 (96.0)
≥ 8 Weeks	1337 (92.2)	2182 (92.6)	3756 (91.9)
≥ 12 Weeks	1267 (87.4)	2125 (90.2)	3609 (88.3)
≥ 24 Weeks	1024 (70.6)	1930 (81.9)	3049 (74.6)
≥ 32 Weeks	835 (57.6)	1683 (71.4)	2561 (62.6)
≥ 52 Weeks	510 (35.2)	1107 (47.0)	1631 (39.9)
≥ 78 Weeks	180 (12.4)	390 (16.5)	575 (14.1)
≥ 91 Weeks	88 (6.1)	171 (7.3)	264 (6.5)
≥ 104 Weeks	39 (2.7)	68 (2.9)	112 (2.7)

APR 10/20/30 BID = apremilast 10/20/30 mg twice daily; APR 20/40 QD = apremilast 20/40 mg once daily.
a The APR Total group includes all apremilast treatment groups (APR 10 BID, APR 20 QD, APR 20 BID, APR 40 QD, and APR 30 BID).
b Exposure is based on each subject's total exposure to apremilast product which is defined as the time interval between the date of the first dose of apremilast and the date of the last dose of apremilast, inclusive. Duration of placebo treatment during the Randomized Treatment Withdrawal Phase in studies PSOR-008 and PSOR-009 was excluded from apremilast exposure. For ongoing subjects, the last dose date was imputed as the minimum of the cutoff date and the last (either start or end) date among visit dates, dosing dates, AE dates, concomitant medication dates, and drug dispensed dates.
Note: Studies PSA-002, PSA-003, PSA-004, PSA-005, and RA-002 include all apremilast exposure data through the cutoff date for subjects who received apremilast without regard to when the subject was randomized to apremilast.
Subjects in Studies PSA-001, PSOR-004, and PSOR-005-E-LTE were not required to enter the extension phases in these studies; therefore, the decrease in numbers in this table does not necessarily reflect treatment discontinuations but is instead a consequence of study designs.

Demographics

The demographic characteristics of subjects at baseline in the Apremilast Data Pool were generally well balanced across treatment groups (Table 60). The majority of subjects were white (93.5%) and not Hispanic (88.0%), and 54.3% were male. Subjects ranged in age from 18 to 85 years; the overall median age was 49.0 years. Subjects' median weight was 85.00 kg and subjects' median BMI was 29.30 kg/m^2. Approximately half of the subjects were enrolled in North America (50.9%), 35.9% were enrolled in Europe, and 13.2% were enrolled in the Rest of the World.

Table 60: Apremilast Data Pool: Baseline Demographics (Subjects as Initially Treated at Week 0)

Demographic	Placebo (N=1411)	APR 20 BID (N=1029)	APR 30 BID (N=1668)	Total[a] (N=4370)
Age (years)				
n	1411	1029	1668	4370
Mean (SD)	48.8 (12.56)	49.8 (12.28)	47.7 (12.81)	48.4 (12.63)
Median	49.0	50.0	48.0	49.0
Min, Max	18, 83	18, 85	18, 83	18, 85
Age Category 1 (years), n (%)				
< 65	1268 (89.9)	915 (88.9)	1509 (90.5)	3936 (90.1)
≥ 65	143 (10.1)	114 (11.1)	159 (9.5)	434 (9.9)
Age Category 2 (years), n (%)				
< 40	336 (23.8)	208 (20.2)	455 (27.3)	1079 (24.7)
40 — < 65	932 (66.1)	707 (68.7)	1054 (63.2)	2857 (65.4)
65 — < 75	120 (8.5)	98 (9.5)	150 (9.0)	384 (8.8)
75 — < 85	23 (1.6)	15 (1.5)	9 (0.5)	49 (1.1)
≥ 85	0	1 (0.1)	0	1 (<0.1)
Sex, n (%)				
Male	779 (55.2)	495 (48.1)	926 (55.5)	2372 (54.3)
Female	632 (44.8)	534 (51.9)	742 (44.5)	1998 (45.7)
Race, n (%)				
White	1323 (93.8)	977 (94.9)	1546 (92.7)	4087 (93.5)
Asian	46 (3.3)	27 (2.6)	54 (3.2)	135 (3.1)
Black or African American	19 (1.3)	5 (0.5)	39 (2.3)	68 (1.6)
American Indian or Alaska Native	7 (0.5)	2 (0.2)	5 (0.3)	16 (0.4)
Native Hawaiian or Other Pacific Islander	4 (0.3)	2 (0.2)	7 (0.4)	13 (0.3)
Other	10 (0.7)	13 (1.3)	17 (1.0)	42 (1.0)
Missing	2 (0.1)	3 (0.3)	0	9 (0.2)
Ethnicity, n (%)[b]				
Hispanic or Latino	72 (5.1)	38 (3.7)	101 (6.1)	223 (5.1)
Not Hispanic or Latino	1252 (88.7)	879 (85.4)	1567 (93.9)	3846 (88.0)
Missing	87 (6.2)	112 (10.9)	0	301 (6.9)
Region, n (%)				
North America	689 (48.8)	423 (41.1)	952 (57.1)	2226 (50.9)
Europe	528 (37.4)	446 (43.3)	494 (29.6)	1568 (35.9)
Rest of the World	194 (13.7)	160 (15.5)	222 (13.3)	576 (13.2)
Weight (kg)				
n	1411	1027	1668	4368
Mean (SD)	87.64 (21.346)	85.44 (20.578)	88.70 (21.476)	87.76 (21.258)
Median	85.00	83.00	87.00	85.00
Min, Max	43.5, 191.1	40.8, 181.4	45.0, 196.0	40.8, 196.0
Weight Category (kg)				
< 70	276 (19.6)	215 (20.9)	323 (19.4)	845 (19.3)

Subject Disposition

PsA Phase 3 Data Pool

In total, 2019 subjects were randomized and received at least one dose of IP; 671 subjects received placebo and 1348 subjects received apremilast (APR Total group) (Table 61). Of these, 89.0% of subjects receiving placebo and 83.8% of subjects receiving apremilast completed the placebo-controlled phase.

The most frequently cited reasons for study discontinuation were AEs, withdrawal by the subject, and lack of efficacy.

Table 61: PsA Phase 3 Data Pool: Subject Disposition During the Placebo-controlled Phase (Subjects as Initially Treated at Week 0)

	Placebo (N=671) n (%)	APR 20 BID (N=676) n (%)	APR 30 BID (N=672) n (%)	APR Total (N=1348) n (%)
Safety Population[a]	671 (100)	676 (100)	672 (100)	1348 (100)
Disposition				
Completed	597 (89.0)	563 (83.3)	567 (84.4)	1130 (83.8)
Discontinued	68 (10.1)	79 (11.7)	82 (12.2)	161 (11.9)
Primary reason for discontinuation				
Adverse event	23 (3.4)	29 (4.3)	36 (5.4)	65 (4.8)
Lack of efficacy	11 (1.6)	15 (2.2)	15 (2.2)	30 (2.2)
Noncompliance with study drug	0	2 (0.3)	3 (0.4)	5 (0.4)
Withdrawal by subject	20 (3.0)	22 (3.3)	16 (2.4)	38 (2.8)
Death	0	1 (0.1)	0	1 (0.1)
Lost to follow up	7 (1.0)	2 (0.3)	7 (1.0)	9 (0.7)
Protocol violation	2 (0.3)	1 (0.1)	2 (0.3)	3 (0.2)
Other	5 (0.7)	7 (1.0)	3 (0.4)	10 (0.7)
Completed and did not enter the next treatment period[b]	6 (0.9)	34 (5.0)	23 (3.4)	57 (4.2)

APR 20/30 BID = apremilast 20/30 mg twice daily; PsA = psoriatic arthritis.
a Includes subjects who were randomized and received at least one dose of investigational product.
b Includes subjects who completed the assessments associated with the last visit of the Placebo-controlled Period but did not continue into the active treatment phase.
Note: Placebo-controlled Period includes data during the placebo-controlled phase of each study. Only data up to Week 16 were included for placebo-treated subjects who escaped early, whereas data up to Week 24 were included for all other subjects.

PSOR Phase 3 Data Pool

For the PSOR Phase 3 Data Pool, 418 subjects received placebo and 832 subjects received APR 30 BID during the Treatment Duration Period Weeks 0 to 16 (Table 62). Of these, 84.2% of subjects in the placebo group and 86.9% of subjects in the APR 30 BID group completed the Treatment Duration Period Weeks 0 to 16. The most frequently cited reasons for study discontinuation were AEs, withdrawal by the subject, lost to follow-up, and lack of efficacy.

Table 62: PSOR Phase 3 Data Pool: Disposition of Subjects During the Treatment Duration Period Weeks 0 to 16 (Subjects as Initially Treated at Week 0)

Disposition	Placebo (N=418) n (%)	APR 30 BID (N=832) n (%)
Safety Population[a]	418 (100)	832 (100)
Disposition		
Completed	352 (84.2)	723 (86.9)
Discontinued	58 (13.9)	95 (11.4)
Primary Reason for Discontinuation		
Adverse event	14 (3.3)	36 (4.3)
Lack of efficacy	9 (2.2)	5 (0.6)
Noncompliance with study drug	0	7 (0.8)
Withdrawal by subject	16 (3.8)	20 (2.4)
Death	1 (0.2)	0
Lost to follow-up	15 (3.6)	17 (2.0)
Protocol violation	1 (0.2)	8 (1.0)
Other	2 (0.5)	2 (0.2)
Completed and did not enter the next treatment period[b]	8 (1.9)	14 (1.7)

APR 30 BID = apremilast 30 mg twice daily; PSOR = psoriasis.
a Includes subjects who were randomized and received at least 1 dose of investigational product.
b Includes subjects who completed the assessments associated with the last visit of the Placebo-controlled Period, but who did not continue into the active treatment phase.
Note: For Subjects as Initially Treated at Week 0, data up to the Week 16 visit are included.

- Apremilast Data Pool

A total of 4089 apremilast subjects were included in the Apremilast-exposure Period in the Apremilast Data Pool. As of the cutoff date, 46.1% of apremilast-treated subjects remain in the studies, 42.2% have discontinued, and 7.4% have completed their study. The most frequently cited reasons for study discontinuation were lack of efficacy, withdrawal by the subject, and AEs. Overall, 8.0% of apremilast

subjects have discontinued study drug due to AE (APR Total group), including 7.4% and 8.5% of subjects in the APR 20 BID and APR 30 BID treatment groups, respectively.

Table 63: PSOR Phase 3 Data Pool: Disposition of Subjects During the Treatment Duration Period Weeks 0 to 16 (Subjects as Initially Treated at Week 0)

Disposition	Placebo (N=418) n (%)	APR 30 BID (N=832) n (%)
Safety Population[a]	418 (100)	832 (100)
Disposition		
Completed	352 (84.2)	723 (86.9)
Discontinued	58 (13.9)	95 (11.4)
Primary Reason for Discontinuation		
Adverse event	14 (3.3)	36 (4.3)
Lack of efficacy	9 (2.2)	5 (0.6)
Noncompliance with study drug	0	7 (0.8)
Withdrawal by subject	16 (3.8)	20 (2.4)
Death	1 (0.2)	0
Lost to follow-up	15 (3.6)	17 (2.0)
Protocol violation	1 (0.2)	8 (1.0)
Other	2 (0.5)	2 (0.2)
Completed and did not enter the next treatment period[b]	8 (1.9)	14 (1.7)

APR 30 BID = apremilast 30 mg twice daily; PSOR = psoriasis.
a Includes subjects who were randomized and received at least 1 dose of investigational product.
b Includes subjects who completed the assessments associated with the last visit of the Placebo-controlled Period, but who did not continue into the active treatment phase.
Note: For Subjects as Initially Treated at Week 0, data up to the Week 16 visit are included.

Medical History

PsA Phase 3 Data Pool

The reported medical history of subjects in the PsA Phase 3 Data Pool was consistent with the disease population and known comorbidities and was generally well balanced across treatment groups. Overall, 91.4% of subjects reported at least one medical history condition. A substantial percentage of the subject population had a history of cardiovascular conditions. Individual cardiovascular risk factors included hypertension (38.2%), hypercholesterolemia (13.7%), obesity (11.0%), hyperlipidemia (8.4%) and type 2 diabetes mellitus (6.6%). Another known comorbidity of psoriatic arthritis is depression, which was reported by 13.6% of subjects. Other common medical history conditions included menopause (12.8%), osteoarthritis (12.5%), gastroesophageal reflux disease (11.6%), postmenopause (10.5%), drug hypersensitivity (10.3%), and hysterectomy (10.1%). All other medical history conditions were reported in <10% of subjects in the PsA Phase 3 Data Pool.

PSOR Phase 3 Data Pool

Overall, 89.8% of subjects reported at least one medical history condition. A substantial percentage of the subjects had a history of cardiovascular conditions. Individual cardiovascular risk factors included hypertension (31.3%), obesity (15.3%), hyperlipidemia (12.6%), type 2 diabetes mellitus (10.1%), and hypercholesterolemia (9.8%).Another known comorbidity of PSOR is depression, which was reported by 13.6% of all subjects. Other common medical history conditions included seasonal allergy (12.9%), drug hypersensitivity (11.0%), and gastroesophageal reflux disease (10.6%). All other medical history conditions were reported in <10% of subjects in the PSOR Phase 3 Data Pool.

Apremilast Data Pool

Overall, 89.9% of subjects reported at least one medical history condition. A substantial percentage of the subject population had a history of cardiovascular conditions. Individual cardiovascular risk factors included hypertension (34.0%), hypercholesterolemia (11.3%), obesity (10.7%), hyperlipidemia (9.2%), and type 2 diabetes mellitus (7.3%). Another known comorbidity of psoriatic arthritis and psoriasis is depression, which was reported by 13.4% of subjects. Other common medical history conditions included

gastroesophageal reflux disease (11.0%), osteoarthritis (10.8%) and drug hypersensitivity (10.1%). All other medical history conditions were reported in <10% of subjects in the Apremilast Data Pool.

Concomitant Medications

PsA Phase 3 Data Pool

The majority of subjects in the PsA Phase 3 Data Pool took concomitant medications during the Placebo-controlled Period (96.0%, placebo group; 97.1%, APR Total group).

With the exception of PSA-005, where apremilast was evaluated as monotherapy, subjects were allowed to continue use of stable baseline doses of small-molecule DMARDs, oral corticosteroids, and/or nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly per protocol. The percentage of subjects receiving concomitant therapy was generally consistent across treatment groups.

The most frequently reported concomitant medications were anti-inflammatory and antirheumatic products (67.1%, placebo group; 69.6%, APR Total group), antipsoriatics (44.7%, placebo group; 43.5%, APR Total group), all other therapeutic products (39.3%, placebo group; 39.5%, APR Total group), drugs for acid related disorders (27.6%, placebo group; 32.3%, APR Total group), analgesics (25.9%, placebo group; 30.9%, APR Total group), and lipid modifying agents (21.9%, placebo group; 20.5%, APR Total group). All other classes of concomitant medications were used by <20% of subjects in the placebo or APR total groups. Similar patterns of concomitant medication use were observed for Apremilast Subjects as Treated during the Apremilast-exposure Period in the PsA Phase 3 Data Pool.

PSOR Phase 3 Data Pool

The majority of subjects in the PSOR Phase 3 Data Pool took concomitant medications during the Treatment Duration Period Weeks 0 to 16 (82.1%, placebo group; 84.5%, APR 30 BID group). The most frequently reported concomitant medications were analgesics (Placebo, 25.8%; APR 30 BID, 29.3%) and anti-inflammatory and antirheumatic products (Placebo, 23.4%; APR 30 BID, 29.8%). Similar patterns of concomitant medication use were observed for Apremilast Subjects as Treated during the Apremilast-exposure Period in the PSOR Phase 3 Data Pool.

Apremilast Data Pool

The majority of subjects in the Apremilast Data Pool, for Subjects as Initially Treated at Week 0, took concomitant medications (88.7%, placebo group; 90.4%, APR Total group).

The percentage of subjects receiving concomitant therapy was generally consistent across treatment groups. The most frequently reported concomitant medications were anti-inflammatory and antirheumatic products (50.8%, placebo group; 53.1%, APR Total group), analgesics (27.1%, placebo group; 31.0%, APR Total group), drugs for acid related disorders (22.5, placebo group; 25.1%, APR Total group), agents acting on the renin-angiotensin system (25.7%, placebo group; 24.5%, APR Total group), all other therapeutic products (24.9%, placebo group; 24.3%, APR Total group), antipsoriatics (23.6%, placebo group; 21.7%, APR Total group), and lipid modifying agents (20.1%, placebo group; 19.6%, APR Total group). All other classes of concomitant medications were used by < 20% of subjects in either the placebo or APR total groups.

Similar patterns of concomitant medication use were observed in Apremilast Subjects as Treated during the Apremilast Data Pool for the Apremilast-exposure Period.

Adverse events

PsA Phase 3 Data Pool

- Treatment Duration Period Weeks 0 to 16

An overview of TEAEs during the Treatment Duration Period Weeks 0 to 16 in the PsA Phase 3 Data Pool is presented in Table 64. The subject incidence of at least one TEAE or TEAEs leading to drug withdrawal was higher in subjects treated with apremilast than subjects receiving placebo, with a trend suggesting a dose effect. The percentage of subjects with severe or serious TEAEs was low and there was no clinically meaningful difference between subjects treated with placebo or apremilast or between subjects treated with APR 20 BID or APR 30 BID.

Table 64: PsA Phase 3 Data Pool: Overview of TEAEs During the Treatment Duration Period Weeks 0 to 16

	Subjects as Initially Treated at Week 0		Apremilast Subjects as Treated					
	Placebo (N=671) SY=194.1		APR 20 BID (N=972) SY=279.2		APR 30 BID (N=973) SY=277.7		APR Total (N=1945) SY=556.8	
	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Any TEAE	288 (42.9)	202.9	470 (48.4)	254.6	516 (53.0)	309.1	986 (50.7)	280.5
Any severe TEAE	23 (3.4)	12.0	29 (3.0)	10.5	35 (3.6)	12.8	64 (3.3)	11.7
Any serious TEAE	22 (3.3)	11.5	23 (2.4)	8.3	21 (2.2)	7.6	44 (2.3)	8.0
Any TEAE leading to drug withdrawal	24 (3.6)	12.4	44 (4.5)	15.9	51 (5.2)	18.6	95 (4.9)	17.3

APR = apremilast; BID = twice daily; SY = subject years; TEAE = treatment-emergent adverse event

Note: A TEAE is an adverse event with a start date on or after the date of the first dose of investigational product and no later than 28 days after the last dose of investigational product. Each subject was counted once for each applicable category. Data up to 16 weeks after the apremilast start date were included regardless of when apremilast exposure started (Week 0, Week 16 or Week 24).

Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

- Apremilast-exposure Period

During the Apremilast-exposure Period for the Apremilast Subjects as Treated population, the EAIR per 100 subject-years for TEAEs was 166.0 in the APR Total group; 158.6 in the APR 20 BID group and 174.0 in the APR 30 BID group. During the Treatment Duration Period Weeks 0 to 16 for the Subjects as Treated population, EAIRs per 100 subject-years for TEAEs was 280.5 in the APR Total group; 254.6 in the APR 20 BID group and 309.1 in the APR 30 BID group. The EAIR per 100 subject-years did not increase during the Apremilast exposure Period; therefore, there was no evidence of an increased incidence of TEAEs with longer apremilast exposure. Similarly, there was no evidence of an increased incidence of severe TEAEs, serious TEAEs, or TEAEs leading to drug withdrawal, based on EAIR per 100 subject years.

PSOR Phase 3 Data Pool

Treatment Duration Period Weeks 0 to 16

An overview of TEAEs during the Treatment Duration Period Weeks 0 to 16 in the PSOR Phase 3 Data Pool is presented in Table 65. The subject incidence of at least one TEAE or TEAEs leading to drug withdrawal was higher in subjects treated with APR 30 BID compared with placebo. The percentage of subjects with severe or serious TEAEs was low and there was no clinically meaningful difference between subjects treated with placebo or APR 30 BID. The findings were similar for both the Subjects as Initially Treated at Week 0 and Subjects as Treated populations.

Table 65: PSOR Phase 3 Data Pool: Overview of TEAEs During the Treatment Duration Period Weeks 0 to 16

	Subjects as Initially Treated at Week 0				Apremilast Subjects as Treated	
	Placebo (N=418) SY=116.5		APR 30 BID (N=832) SY=236.8		APR 30 BID (N=1184) SY=338.6	
	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Any TEAE	239 (57.2)	350.3	573 (68.9)	536.4	793 (67.0)	483.8
Any severe TEAE	15 (3.6)	13.0	32 (3.8)	13.7	40 (3.4)	12.0
Any serious TEAE	11 (2.6)	9.5	17 (2.0)	7.2	22 (1.9)	6.5
Any TEAE leading to drug withdrawal	16 (3.8)	13.8	45 (5.4)	19.2	57 (4.8)	17.0
Any TEAE leading to drug interruption	17 (4.1)	14.9	53 (6.4)	23.2	62 (5.2)	18.9

APR 30 BID = apremilast 30 mg twice daily; PSOR = psoriasis; SY = subject-years; TEAE = treatment-emergent adverse event.
Note: For Subjects as Initially Treated at Week 0 data up to the Week 16 visit are included. For Apremilast Subjects as Treated, data for the first 16 weeks of exposure are included regardless of when apremilast exposure started, ie, for subjects treated with apremilast at Week 0, data from study Weeks 0 to 16 are included, whereas for subjects who are first treated with apremilast at Week 16 data from study Weeks 16 to 32 are included.
A TEAE is an adverse event with a start date on or after the date of the first dose of investigational product (IP) and no later than 28 days after the last dose of IP. Each subject is counted once for each applicable category.
Exposure adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

- Apremilast-exposure Period

During the Apremilast-exposure Period for the Apremilast Subjects as Treated population, the EAIR per 100 subject-years for TEAEs was 287.4 in the APR 30 BID group. During the Treatment Duration Period Weeks 0 to 16 for the Subjects as Treated population, EAIRs per 100 subject years for TEAEs was 483.8 in the APR 30 BID group.Based on EAIR per 100 subject-years, there was no evidence of an increased incidence of TEAEs with longer apremilast exposure. Similarly, there was no evidence of an increased incidence of severe TEAEs, serious TEAEs, or TEAEs leading to drug withdrawal, based on EAIR per 100 subject-years.

Apremilast Data Pool

Placebo-controlled Period

An overview of TEAEs during the Placebo-controlled Period for the Apremilast Data Pool is presented in Table 66. At least one TEAE was reported by 53.6% of subjects in the placebo group and 65.2% of subjects in the APR Total group. The subject incidence of at least one TEAE or TEAEs leading to drug withdrawal was higher in the APR Total group than the placebo group, with no clinically meaningful difference between subjects treated with APR 20 BID or APR 30 BID. The percentage of subjects with severe or serious TEAEs was low and there was no clinically meaningful difference between subjects treated with placebo or apremilast or between subjects treated with APR 20 BID or APR 30 BID.

Table 66: Apremilast Data Pool: Overview of Treatment-emergent Adverse Events During the Placebo-controlled Period (Subjects as Initially Treated at Week 0)

	Placebo (N=1411) SY=429.5		APR 20 BID (N=999) SY=377.4		APR 30 BID (N=1668) SY=574.5		APR Total[a] (N=2910) SY=1010.0	
	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Any TEAE	756 (53.6)	272.7	625 (62.6)	296.9	1095 (65.6)	385.8	1897 (65.2)	364.4
Any severe TEAE	60 (4.3)	14.2	36 (3.6)	9.7	77 (4.6)	13.7	128 (4.4)	12.9
Any serious TEAE	49 (3.5)	11.5	34 (3.4)	9.1	45 (2.7)	7.9	80 (2.7)	8.0
Any TEAE leading to drug withdrawal	63 (4.5)	14.7	60 (6.0)	16.0	107 (6.4)	18.8	182 (6.3)	18.2

APR = apremilast; BID = twice daily; EAIR = exposure-adjusted incidence rate; QD = once daily; SY = subject-years; TEAE = treatment-emergent adverse event
[a] The APR Total group includes all apremilast treatment groups (APR 10 BID, APR 20 QD, APR 20 BID, APR 40 QD, and APR 30 BID).
Note: Placebo-controlled period includes data during the placebo-controlled period of each study. In Studies PSA-002, PSA-003, PSA-004, PSA-005, and RA-002, only data up to Week 16 were included for placebo-treated

- Apremilast-exposure Period

An overview of TEAEs during the Apremilast-exposure Period for the Apremilast Data Pool is presented in Table 67. With the additional subject exposure to apremilast, there was no evidence of an increased incidence of TEAEs, severe TEAEs, serious TEAEs, or TEAEs leading to drug withdrawal, based on EAIR per 100 subject-years.

Table 67: Apremilast Data Pool: Overview of Treatment-emergent Adverse Events During the Apremilast-exposure Period (Apremilast Subjects as Treated)

	APR 20 BID (N=1450) SY=1185.3		APR 30 BID (N=2357) SY=2241.5		APR Total[a] (N=4089) SY=3541.0	
	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Any TEAE	1007 (69.4)	194.4	1801 (76.4)	231.7	3029 (74.1)	227.5
Any severe TEAE	98 (6.8)	8.6	191 (8.1)	8.9	318 (7.8)	9.3
Any serious TEAE	94 (6.5)	8.1	139 (5.9)	6.4	240 (5.9)	6.9
Any TEAE leading to drug withdrawal	112 (7.7)	9.5	200 (8.5)	9.0	333 (8.1)	9.5

APR = apremilast; BID = twice daily; EAIR = exposure-adjusted incidence rate; QD = once daily; SY = subject-years; TEAE = treatment-emergent adverse event

[a] The APR Total group includes all apremilast treatment groups (APR 10 BID, APR 20 QD, APR 20 BID, APR 40 QD, and APR 30 BID).

Note: Apremilast exposure includes all data while subjects were exposed to apremilast regardless of when the apremilast exposure started. A TEAE is an adverse event with a start date on or after the date of the first dose of apremilast and no later than 28 days after the last dose of apremilast.

Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

In Studies PSOR-008 and PSOR-009, adverse events that started 28 days after initiating placebo and before resuming apremilast treatment in the Randomized Treatment Withdrawal Phase (Week 32 to 52) were excluded. Duration of placebo treatment in the withdrawal phase was excluded from apremilast exposure. Each subject was counted once for each applicable category.

Common Adverse Events

The most frequently reported TEAEs during the Placebo-controlled Period were gastrointestinal disorders (diarrhoea, nausea), infections and infestations (URTIs, nasopharyngitis) and nervous system disorders (headache, tension headache).

A treatment and dose effect was observed for gastrointestinal disorders and nervous system disorders, but not for infections and infestations.

The pattern of TEAEs was similar in the PsA and PSOR Phase 3 studies. The EAIRs per 100 subject-years for each of the 6 frequently reported TEAEs in apremilast-treated subjects did not increase during the Apremilast-exposure Period; therefore, there is no evidence that the incidence of these events increases with longer apremilast exposure.

PsA Phase 3 Data Pool

Treatment Duration Period Weeks 0 to 16

In the PsA Phase 3 Data Pool, the SOCs with the highest subject incidence of TEAEs during the Treatment Duration Period Weeks 0 to 16, were gastrointestinal disorders, infections and infestations and nervous system disorders. The proportions of subjects reporting TEAEs in the SOCs of gastrointestinal disorders and nervous system disorders were higher in the apremilast groups than the placebo group, with a trend suggesting a dose effect.

There was no notable difference between the placebo and apremilast groups in the percentage of subjects reporting TEAEs in the SOC of infections and infestations and there was no evidence of a dose effect. Investigations and cardiac disorders were also reported in a higher percentage of subjects in the apremilast groups than the placebo group.

A summary of TEAEs with subject incidence of at least 2% in any treatment group during the Treatment Duration Period Weeks 0 to 16 in the PsA Phase 3 Data Pool is presented in Table 68. The most frequently reported TEAEs were diarrhoea, nausea, headache, and upper respiratory tract infection, which is consistent with the most frequently, reported SOCs listed above. These TEAEs were reported at a higher frequency in the APR Total group than the placebo group. The subject incidence of diarrhoea, nausea, and

headache was higher in the APR 30 BID group than in the APR 20 BID group, suggesting a dose effect. A dose effect was not observed for upper respiratory tract infection.

Table 68: PsA Phase 3 Data Pool: TEAEs with Subject Incidence of at Least 2% in any Treatment Group During the Treatment Duration Period Weeks 0 to 16

	Subjects as Initially Treated at Week 0								Apremilast Subjects as Treated					
	Placebo (N=671) SY=194.1		APR 20 BID (N=676) SY=196.7		APR 30 BID (N=672) SY=192.3		APR Total (N=1348) SY=388.9		APR 20 BID (N=972) SY=279.2		APR 30 BID (N=973) SY=277.7		APR Total (N=1945) SY=556.8	
Preferred Term[a]	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Any TEAE	288 (42.9)	202.9	351 (51.9)	283.5	365 (54.3)	326.8	716 (53.1)	304.0	470 (48.4)	254.6	516 (53.0)	309.1	986 (50.7)	280.5
Diarrhoea	17 (2.5)	8.9	66 (9.8)	36.4	103 (15.3)	60.6	169 (12.5)	48.1	86 (8.8)	33.2	128 (13.2)	51.3	214 (11.0)	42.0
Nausea	26 (3.9)	13.7	64 (9.5)	35.3	101 (15.0)	59.4	165 (12.2)	46.9	71 (7.3)	27.0	114 (11.7)	45.1	185 (9.5)	35.9
Headache	24 (3.6)	12.7	44 (6.5)	23.6	66 (9.8)	36.8	110 (8.2)	30.1	53 (5.5)	19.8	77 (7.9)	29.4	130 (6.7)	24.6
Upper respiratory tract infection	16 (2.4)	8.4	31 (4.6)	16.2	27 (4.0)	14.4	58 (4.3)	15.3	42 (4.3)	15.4	37 (3.8)	13.6	79 (4.1)	14.5
Vomiting	5 (0.7)	2.6	16 (2.4)	8.3	21 (3.1)	11.1	37 (2.7)	9.7	17 (1.7)	6.2	29 (3.0)	10.6	46 (2.4)	8.4
Nasopharyngitis	12 (1.8)	6.2	17 (2.5)	8.8	15 (2.2)	7.9	32 (2.4)	8.3	28 (2.9)	10.2	17 (1.7)	6.2	45 (2.3)	8.2
Hypertension	15 (2.2)	7.8	11 (1.6)	5.6	13 (1.9)	6.8	24 (1.8)	6.2	17 (1.7)	6.1	25 (2.6)	9.1	42 (2.2)	7.6
Dyspepsia	8 (1.2)	4.2	19 (2.8)	9.9	11 (1.6)	5.8	30 (2.2)	7.8	21 (2.2)	7.6	19 (2.0)	6.9	40 (2.1)	7.3
Abdominal pain upper	1 (0.1)	0.5	14 (2.1)	7.2	18 (2.7)	9.5	32 (2.4)	8.4	19 (2.0)	6.9	18 (1.8)	6.6	37 (1.9)	6.7
Abdominal pain	8 (1.2)	4.1	9 (1.3)	4.6	15 (2.2)	7.9	24 (1.8)	6.2	14 (1.4)	5.1	18 (1.8)	6.6	32 (1.6)	5.8

APR= apremilast; BID= twice daily; PsA = psoriatic arthritis; PT = preferred term; SY = subject-years; TEAE = treatment-emergent adverse event.
a Preferred terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA)Version 14.0. Preferred terms are sorted in descending order of subject incidence of the APR Total column for the Apremilast Subjects as Treated population.
Note: A TEAE is an adverse event with a start date on or after the date of the first dose of investigational product (IP) and no later than 28 days after the last dose of IP. Subjects with multiple TEAEs within a PT were counted once for that PT. Data up to 16 weeks after the apremilast start date were included regardless of when apremilast exposure started (Week 0, Week 16, or Week 24).
Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

- Apremilast-exposure Period

The most frequently reported TEAEs in the PsA Phase 3 Data Pool during the Apremilast-exposure Period were the same as those reported during the Treatment Duration Period Weeks 0 to 16, ie, diarrhea, nausea, upper respiratory tract infection, and headache. During the Treatment Duration Period Weeks 0 to 16 the EAIRs per 100 subject-years for the frequently reported TEAEs in the APR treatment groups were higher than those during the Apremilast-exposure Period. Based on EAIR per 100 subject-years, there is no evidence of an increased incidence of frequently reported TEAEs with longer exposure to apremilast.

PSOR Phase 3 Data Pool

Treatment Duration Period Weeks 0 to 16

In the PSOR Phase 3 Data Pool, the system organ classes (SOCs) with the highest subject incidence of TEAEs during the Treatment Duration Period Weeks 0 to 16 were gastrointestinal disorders, infections and infestations, and nervous system disorders. The proportions of subjects reporting a TEAE in the SOCs of gastrointestinal disorders and nervous system disorders were higher in the APR 30 BID group than in the placebo group. The percentage of subjects reporting infections and infestations was similar in the APR 30 BID and the placebo groups.

A summary of TEAEs with subject incidence of at least 2% in any treatment group during the Treatment Duration Period Weeks 0 to 16 in the PSOR Phase 3 Data Pool is presented in Table 69. The most frequently reported TEAEs were diarrhoea, nausea, upper respiratory tract infection, nasopharyngitis, tension headache, and headache, which is consistent with the most frequently reported SOCs listed above. The subject incidence of diarrhoea, nausea, upper respiratory tract infection, tension headache, and headache was higher in the APR 30 BID group than in the placebo group.

Table 69: PSOR Phase 3 Data Pool: TEAEs with Subject Incidence of at Least 2% in any Treatment Group During the Treatment Duration Period Weeks 0 to 16

	Subjects as Initially Treated at Week 0				Apremilast Subjects as Treated	
	Placebo (N=418) SY=116.5		APR 30 BID (N=832) SY=236.8		APR 30 BID (N=1184) SY=338.6	
Preferred Term[a]	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Any TEAE	239 (57.2)	350.3	573 (68.9)	536.4	793 (67.0)	483.8
Diarrhoea	28 (6.7)	25.5	148 (17.8)	74.2	186 (15.7)	63.3
Nausea	28 (6.7)	25.3	138 (16.6)	68.2	164 (13.9)	55.1
Upper respiratory tract infection	27 (6.5)	23.9	70 (8.4)	30.9	100 (8.4)	30.9
Nasopharyngitis	29 (6.9)	25.9	61 (7.3)	26.8	89 (7.5)	27.4
Tension headache	14 (3.3)	12.4	61 (7.3)	27.5	85 (7.2)	26.8
Headache	14 (3.3)	12.4	48 (5.8)	21.2	59 (5.0)	18.1
Vomiting	7 (1.7)	6.1	31 (3.7)	13.4	39 (3.3)	11.8
Fatigue	6 (1.4)	5.2	25 (3.0)	10.8	32 (2.7)	9.6
Dyspepsia	4 (1.0)	3.5	25 (3.0)	10.8	31 (2.6)	9.4
Decreased appetite	4 (1.0)	3.5	23 (2.8)	9.9	28 (2.4)	8.4
Arthralgia	7 (1.7)	6.1	14 (1.7)	6.0	25 (2.1)	7.5
Sinusitis	6 (1.4)	5.2	18 (2.2)	7.7	25 (2.1)	7.5
Back pain	4 (1.0)	3.5	20 (2.4)	8.5	25 (2.1)	7.5
Migraine	4 (1.0)	3.4	17 (2.0)	7.3	25 (2.1)	7.5
Abdominal discomfort	6 (1.4)	5.2	18 (2.2)	7.7	24 (2.0)	7.2
Frequent bowel movements	1 (0.2)	0.9	17 (2.0)	7.3	24 (2.0)	7.2
Abdominal pain	6 (1.4)	5.2	17 (2.0)	7.3	22 (1.9)	6.6
Insomnia	4 (1.0)	3.5	20 (2.4)	8.6	22 (1.9)	6.6
Abdominal pain upper	4 (1.0)	3.5	18 (2.2)	7.7	21 (1.8)	6.3
Hypertension	10 (2.4)	8.7	14 (1.7)	6.0	20 (1.7)	6.0
Gastroenteritis	9 (2.2)	7.8	13 (1.6)	5.5	20 (1.7)	6.0
Urinary tract infection	9 (2.2)	7.8	16 (1.9)	6.8	17 (1.4)	5.1
Psoriasis	13 (3.1)	11.3	8 (1.0)	3.4	10 (0.8)	3.0

APR 30 BID = apremilast 30 mg twice daily; PSOR = psoriasis; SY = subject-years; TEAE = treatment-emergent adverse event.
a Preferred terms were coded using the Medical Dictionary for Regulatory Activities (Version 14.0) and are sorted in descending order of subject incidence of the Apremilast Subjects as Treated column.
Note: For Subjects as Initially Treated at Week 0 data up to the Week 16 visit are included. For Apremilast Subjects as Treated, data for the first 16 weeks of exposure are included regardless of when apremilast exposure started, ie, for subjects treated with apremilast at Week 0, data from study Weeks 0 to 16 are included, whereas for subjects who are first treated with apremilast at Week 16 data from study Weeks 16 to 32 are included.
A TEAE is an adverse event with a start date on or after the date of the first dose of investigational product (IP) and no later than 28 days after the last dose of IP. Each subject is counted once for each applicable specific TEAE.
Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

- Apremilast-exposure Period

The most frequently reported TEAEs in the PSOR Phase 3 Data Pool during the Apremilast-exposure Period were the same as those reported during the Treatment Duration Period Weeks 0 to 16, i.e., diarrhoea, upper respiratory tract infection, nausea, nasopharyngitis, tension headache, and headache. During the Treatment Duration Period Weeks 0 to 16 the EAIRs per 100 subject-years for the frequently reported TEAEs in the APR 30 BID group were higher than those during the Apremilast-exposure Period. Based on EAIR per 100 subject-years, there is no evidence of an increased incidence of the frequently reported TEAEs with longer exposure to apremilast.

- Apremilast Data Pool

Placebo-controlled Period

The most frequently reported TEAEs were diarrhoea, nausea, headache, upper respiratory tract infection, and nasopharyngitis. Of these, diarrhoea, nausea, headache, and upper respiratory tract infections occurred more frequently in the APR Total group than the placebo group, and a dose effect was observed for diarrhoea, nausea, and upper respiratory tract infection. Other frequently reported GI TEAEs also showed treatment effects (e.g., vomiting, upper abdominal pain, dyspepsia, and abdominal pain). Tension headache also occurred more frequently in the APR Total group than the placebo group.

- Apremilast-exposure Period

The most frequently reported TEAEs in the Apremilast Data Pool during the Apremilast-exposure Period were the same as those reported during the Placebo-controlled Period. Based on EAIR per 100

subject-years, there is no evidence of an increased incidence of these most frequently reported TEAEs with longer exposure to apremilast.

Serious adverse event / deaths / other significant events
Treatment-emergent Adverse Events by Severity

PsA Phase 3 Data Pool

In the PsA Phase 3 Data Pool, during the Treatment Duration Period Weeks 0 to 16, TEAEs were predominantly mild or moderate in severity. The percentage of subjects reporting severe TEAEs was 3.4% in the Placebo group, 3.0% in the APR 20 BID group, and 3.6% in the APR 30 BID group.

Diarrhoea, nausea, headache, and upper respiratory tract infection, the most frequently reported TEAEs in the PsA Phase 3 Data Pool, were predominantly mild in severity. Severe diarrhoea occurred in 0.1%, 0.4%, and 0.3% of subjects in the Placebo, APR 20 BID, and APR 30 BID groups, respectively. Severe nausea occurred in 0%, 0.2%, and 0.3% of subjects in the Placebo, APR 20 BID, and APR 30 BID groups, respectively. Severe headache occurred in 0.1%, 0.2%, and 0.1% of subjects in the Placebo, APR 20 BID, and APR 30 BID groups, respectively. No severe upper respiratory tract infection was reported during Treatment Duration Period Weeks 0 to 16.

- Apremilast-exposure Period

In the PsA Phase 3 Data Pool, the percentage of subjects reporting severe TEAEs was 6.2% in the APR 20 BID group and 7.2% in the APR 30 BID group. During the Apremilast-exposure Period for the Apremilast Subjects as Treated population, the EAIR per 100 subject-years for severe TEAEs was 6.6 in the APR 20 BID group and 7.7 in the APR 30 BID group. During the Treatment Duration Period Weeks 0 to 16 for the Subjects as Treated population, EAIR per 100 subject years for severe TEAEs was 10.5 in the APR 20 BID group and 12.8 in the APR 30 BID group. Based on EAIR per 100 subject-years, there was no evidence of an increased incidence of severe TEAEs in the PsA Phase 3 Data Pool with longer apremilast exposure.

PSOR Phase 3 Data Pool

- Treatment Duration Period Weeks 0 to 16

In the PSOR Phase 3 Data Pool, during the Treatment Duration Period Weeks 0 to 16, TEAEs were predominantly mild or moderate in severity. The percentage of subjects reporting severe TEAEs was 3.6% in the placebo group and 3.4% in the APR 30 BID group.

Diarrhoea, nausea, upper respiratory tract infection, nasopharyngitis, tension headache, and headache, the most frequently reported TEAEs during the Treatment Duration Period Weeks 0 to 16 in the PSOR Phase 3 Data Pool, were predominantly mild in severity Severe diarrhoea and nausea were each reported by 1 (0.2%) subject in the placebo group and 3 (0.3%) subjects in the APR 30 BID group. Severe headache (4 [0.3%] subjects), severe tension headache (1 [0.1%] subject), and severe upper respiratory tract infection (1 [0.1%] subject) were reported in the APR 30 BID group only. No events of severe nasopharyngitis were reported in either treatment group.

- Apremilast-exposure Period

In the PSOR Phase 3 Data Pool, during the Apremilast-exposure Period, TEAEs were predominantly mild or moderate in severity. The percentage of subjects in the APR 30 BID group reporting severe TEAEs was 8.2%.

During the Apremilast-exposure Period for the Apremilast Subjects as Treated population, the EAIR per 100 subject-years for severe TEAEs was 8.9 in the APR 30 BID group. During the Treatment Duration Period Weeks 0 to 16 for the Apremilast Subjects as Treated population, EAIR per 100 subject-years for

severe TEAEs was 12.0 in the APR 30 BID group. Based on EAIR per 100 subject-years, there was no evidence of an increased incidence of severe TEAEs in the PSOR Phase 3 Data Pool with longer apremilast exposure.

The majority of severe TEAEs were reported by 1 (0.1%) subject each.

Diarrhoea, upper respiratory tract infection, nausea, nasopharyngitis, tension headache, and headache, the most frequently reported TEAEs during the Apremilast-exposure Period, were predominantly mild in severity. Severe diarrhoea and severe nausea were each reported by 0.3% of subjects and severe tension headache and severe upper respiratory tract infection were each reported by 0.2% of subjects. The only other severe events that were reported by more than 0.2% of subjects were psoriasis (0.5%), headache (0.4%), migraine (0.4%), vomiting (0.3%), and fall (0.3%).

- Apremilast Data Pool

In the Apremilast Data Pool, during the Apremilast-exposure Period, TEAEs were predominantly mild or moderate in severity. The percentage of subjects reporting severe TEAEs was 6.8% in the APR 20 BID group and 8.1% in the APR 30 BID group.

During the Apremilast-exposure Period for the Apremilast Subjects as Treated population, the EAIR per 100 subject-years for severe TEAEs was 8.6 in the APR 20 BID group and 8.9 in the APR 30 BID group. During the Placebo-controlled Period for the Subjects as Initially Treated at Week 0 population, EAIR per 100 subject-years for severe TEAEs was 9.7 in the APR 20 BID group and 13.7 in the APR 30 BID group. Based on EAIR per 100 subject-years, there was no evidence of an increased incidence of severe TEAEs in the Apremilast Data Pool with longer apremilast exposure.

Deaths

As of 31 July 2013, 8 subjects have died during the apremilast clinical program (3 in placebo, 1 in APR 20 BID, and 4 in APR 30 BID). Of these, 7 deaths occurred in applicant's sponsored studies, including 1 death in a PsA study and 6 deaths in psoriasis studies. In addition, 1 death occurred in an investigator-initiated study in RA. There is no pattern associated with cause of death in the apremilast clinical program.

PsA Studies

- In Study PSA-002, a 52-year-old subject who was randomized to the APR 20 BID treatment group, died due to multi-organ failure on Day 73 of the study. The subject had been diagnosed with anaemia due to vitamin B12 deficiency prior to the first dose of apremilast and was also receiving concomitant MTX for the treatment of PsA.

Psoriasis Studies

Placebo

- In Study PSOR-009, a 51-year-old subject, died on Study Day 354 due to intracranial hemorrhage, 130 days after the last dose of APR 30 BID while in the Randomized Treatment Withdrawal Phase. The subject received apremilast for 224 days followed by placebo in the Randomized Treatment Withdrawal Phase. The event occurred on Study Day 353. On Day 352, the subject complained of a headache. The subject was found unresponsive on the floor the following day. A computed tomography scan of the head revealed a large intracranial hematoma in the left hemisphere centered in the basal ganglia region with intraventricular extension and a small bilateral subarachnoid component; midline shift by 1.7 cm as well as evidence of left uncal and tonsilar herniation; and hematoma that filled the third and fourth ventricles. A neurosurgeon

reviewed the imaging and recommended palliative therapy. The subject was pronounced brain dead on Study Day 354.

- In Study PSOR-005-E-LTE, a 63-year-old subject receiving placebo, was found dead with a pink complexion on Study Day 84 in the closed garage with a motorcycle running. An autopsy did not establish cause of death for this subject.
- In Study PSOR-008, a 28-year-old subject, committed suicide via a gunshot wound. The subject was randomized to placebo and had received the last dose on Day 29. The SAE occurred on Study Day 55. The subject's relevant medical history included previous suicide attempts, depression, obesity, unstable family life, alcohol abuse, insomnia, and treatment for bipolar disorder.

Apremilast

- In Study PSOR-004, a 398-pound, 48-year-old subject with psoriasis who was randomized to the APR 20 BID group, had a history of cardiac arrhythmia that was treated with a cardiac ablation procedure. The subject had an unwitnessed death at histhe subject's home 140 days after the start of apremilast treatment and 53 days after the dose was increased from 20 mg BID to 30 mg BID. The cause of death was reported as MI, heart arrhythmia, and hypertensive changes.
- In Study PSOR-008, a 69-year old, white subject, experienced a fatal cerebrovascular accident (CVA) on Study Day 777 while in the long-term extension phase of the study. The subject received placebo in the placebocontrolled treatment phase, followed by APR 30 BID for a total of 666 days. On Study Day 777 (Day 666 on active treatment), while at home, the subject began experiencing symptoms of stroke (not further specified). In the emergency room, the subject was nonresponsive. The subject died in the emergency room due to acute CVA. No treatment was given. The type of stroke (thrombotic or hemorrhagic) was reported as unknown. An autopsy was not performed. A death certificate was not available.
- In Study PSOR-008, a 30-year-old white subject, died on Study Day 111. The subject had received APR 30 BID for a total of 104 days. The subject's medical history included depression, obesity (screening BMI = 35.1 kg/m^2), and alcohol use. One week after the last dose of study drug, the subject was found dead by the subject's partner. No obvious cause of death was identified. The autopsy report revealed diffuse lung congestion and bilateral edema, consistent with acute cardiac failure in association with likely sleep apnea and morbid obesity. At the time of death, the subject's BMI was 40.6 kg/m^2.

Investigator-initiated Studies

- In Study AP-RA-PI-0024, an investigator-initiated study in RA, an 82-year-old subject, died due to acute myeloid leukaemia. The subject received APR 30 BID from 31 Mar 2010 to 28 Jun 2010 (89 days), followed by APR 30 BID or placebo from 28 Jun 2010 to 20 Aug 2010 (53 days). The subject was diagnosed with acute myeloid leukaemia 8 months after the last dose of study medication. The subject had a history of breast cancer and uncontrolled RA for 4 years prior to study entry. Before starting treatment with apremilast, the subject received multiple medications, including adalimumab, MTX, and possibly another TNF blocker (dates not provided). The subject died 20 months after the last dose of apremilast.

Other Serious Adverse Events

Overall, the subject incidence of serious TEAEs (SAEs) was low and comparable between placebo and apremilast treatment groups. The incidence of SAEs was not driven by any single preferred term or specific, individual organ toxicity. Based on EAIR per 100 subject-years, there was no evidence of an increased incidence of SAEs with longer apremilast exposure (Table 70).

Table 70: Apremilast Data Pool: Subject Incidence of Serious TEAEs Reported in 2 or More Subjects in Any Treatment Group During the Apremilast-exposure Period (Subjects as Treated)

	Placebo[a] N=1411 SY=429.5		APR 20 BID N=1450 SY=1185.3		APR 30 BID N=2357 SY=2241.5		APR Total[b] N=4089 SY=3541.0	
Preferred Term[c]	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Any serious TEAE	49 (3.5)	11.5	94 (6.5)	8.1	139 (5.9)	6.4	240 (5.9)	6.9
Psoriatic arthropathy	4 (0.3)	0.9	3 (0.2)	0.3	5 (0.2)	0.2	8 (0.2)	0.2
Osteoarthritis	0	0	2 (0.1)	0.2	5 (0.2)	0.2	7 (0.2)	0.2
Myocardial infarction	1 (0.1)	0.2	2 (0.1)	0.2	4 (0.2)	0.2	6 (0.1)	0.2
Psoriasis	1 (0.1)	0.2	4 (0.3)	0.3	2 (0.1)	0.1	6 (0.1)	0.2
Transient ischaemic attack	0	0	4 (0.3)	0.3	2 (0.1)	0.1	6 (0.1)	0.2
Coronary artery disease	0	0	1 (0.1)	0.1	5 (0.2)	0.2	6 (0.1)	0.2
Intervertebral disc protrusion	1 (0.1)	0.2	2 (0.1)	0.2	3 (0.1)	0.1	5 (0.1)	0.1
Pneumonia	1 (0.1)	0.2	2 (0.1)	0.2	3 (0.1)	0.1	5 (0.1)	0.1
Cholelithiasis	1 (0.1)	0.2	3 (0.2)	0.3	2 (0.1)	0.1	5 (0.1)	0.1
Nephrolithiasis	0	0	1 (0.1)	0.1	4 (0.2)	0.2	5 (0.1)	0.1
Acute myocardial infarction	1 (0.1)	0.2	2 (0.1)	0.2	2 (0.1)	0.1	4 (0.1)	0.1
Atrial fibrillation	0	0	2 (0.1)	0.2	2 (0.1)	0.1	4 (0.1)	0.1
Depression	0	0	2 (0.1)	0.2	2 (0.1)	0.1	4 (0.1)	0.1
Breast cancer	0	0	1 (0.1)	0.1	3 (0.1)	0.1	4 (0.1)	0.1

	Placebo N=1411 SY=429.5		APR 20 BID N=1450 SY=1185.3		APR 30 BID N=2357 SY=2241.5		APR Total N=4089 SY=3541.0	
Preferred Term	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Appendicitis	0	0	2 (0.1)	0.2	2 (0.1)	0.1	4 (0.1)	0.1
Angina pectoris	1 (0.1)	0.2	1 (0.1)	0.1	2 (0.1)	0.1	3 (0.1)	0.1
Prostate cancer	1 (0.1)	0.2	1 (0.1)	0.1	2 (0.1)	0.1	3 (0.1)	0.1
Ankle fracture	1 (0.1)	0.2	2 (0.1)	0.2	1 (<0.1)	0	3 (0.1)	0.1
Hypertension	0	0	2 (0.1)	0.2	1 (<0.1)	0	3 (0.1)	0.1
Abdominal pain	0	0	0	0	3 (0.1)	0.1	3 (0.1)	0.1
Angina unstable	0	0	1 (0.1)	0.1	2 (0.1)	0.1	3 (0.1)	0.1
Pyrexia	0	0	1 (0.1)	0.1	2 (0.1)	0.1	3 (0.1)	0.1
Suicide attempt	0	0	1 (0.1)	0.1	2 (0.1)	0.1	3 (0.1)	0.1
Urinary tract infection	0	0	1 (0.1)	0.1	2 (0.1)	0.1	3 (0.1)	0.1
Inguinal hernia	1 (0.1)	0.2	0	0	2 (0.1)	0.1	2 (<0.1)	0.1
Non-cardiac chest pain	1 (0.1)	0.2	0	0	2 (0.1)	0.1	2 (<0.1)	0.1
Acute respiratory failure	0	0	0	0	2 (0.1)	0.1	2 (<0.1)	0.1
Asthma	0	0	0	0	2 (0.1)	0.1	2 (<0.1)	0.1
Chronic obstructive pulmonary disease	0	0	0	0	2 (0.1)	0.1	2 (<0.1)	0.1
Deep vein thrombosis	0	0	0	0	2 (0.1)	0.1	2 (<0.1)	0.1
Basal cell carcinoma	0	0	2 (0.1)	0.2	0	0	2 (<0.1)	0.1

	Placebo N=1411 SY=429.5		APR 20 BID N=1450 SY=1185.3		APR 30 BID N=2357 SY=2241.5		APR Total N=4089 SY=3541.0	
Preferred Term	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Arterial thrombosis limb	0	0	2 (0.1)	0.2	0	0	2 (<0.1)	0.1
Anxiety	0	0	2 (0.1)	0.2	0	0	2 (<0.1)	0.1
Cardiac failure congestive	1 (0.1)	0.2	2 (0.1)	0.2	0	0	2 (<0.1)	0.1
Myocardial ischaemia	1 (0.1)	0.2	2 (0.1)	0.2	0	0	2 (<0.1)	0.1
Syncope	2 (0.1)	0.5	0	0	1 (<0.1)	0.0	1 (<0.1)	0.0
Hypertensive crisis	2 (0.1)	0.5	0	0	1 (<0.1)	0.0	1 (<0.1)	0.0
Nausea	2 (0.1)	0.5	0	0	1 (<0.1)	0.0	1 (<0.1)	0.0

APR 10/20/30 BID = apremilast 10/20/30 mg twice daily; APR 20/40 QD = apremilast 20/40 mg once daily; SY = subject-years; TEAE = treatment-emergent adverse event.

a Placebo data are from the Placebo-controlled Period, and are provided for purposes of comparison. Subjects who switched from placebo to APR are counted in both the placebo and APR treatment group columns.

b The APR Total group includes all apremilast treatment groups (APR 10 BID, APR 20 QD, APR 20 BID, APR 40 QD, and APR 30 BID).

c Preferred terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0 and sorted in order of decreasing frequency in the APR Total column.

Note: Includes all data while subjects were exposed to investigational product regardless of when exposure started.

A TEAE is an adverse event with a start date on or after the date of the first dose of investigational product (IP) and no later than 28 days after the last dose of IP. In studies PSOR-008 and PSOR-009, adverse events that started 28 days after initiating placebo and before resuming apremilast treatment in the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) were excluded. Duration of placebo treatment in the withdrawal phase was excluded from apremilast exposure. Each subject was counted once for each applicable specific TEAE.

Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

Adjudicated Evaluation of MACE and Potential MACE

Major adverse cardiac events were defined as TEAEs of sudden unwitnessed death, cardiovascular death (sudden cardiac death, death due to MI, death due to heart failure, death due to stroke, and death due to other cardiovascular causes), MI, and nonfatal stroke. Potential MACE was defined as unstable angina requiring hospitalization, coronary revascularization procedure, transient ischemic attack (TIA) and rehospitalisation for recurrent ischemia, embolic events, and deep vein thrombosis.

- Apremilast Data Pool

Events from 8 (0.6%) subjects in the placebo group, 26 (1.8%) subjects in the APR 20 BID group, and 32 (1.4%) subjects in the APR 30 BID group were identified for adjudication of MACE or potential MACE; events from 2 placebo subjects, 3 APR 20 BID subjects, and 4 APR 30 BID subjects were not evaluable. Events were adjudicated as MACE in 0.1% of subjects (1/1411; 0.2 per 100 subject-years) in the placebo group, 0.3% of subjects (5/1450, 0.4 per 100 subject-years) in the APR 20 BID group, and 0.3% of subjects (7/2357; 0.3 per 100 subject-years) in the APR 30 BID group. Events were adjudicated as potential MACE in 0.1% of subjects (2/1411; 0.5 per 100 subject years) in the placebo group, 0.5% of subjects (7/1450; 0.6 per 100 subject-years) in the APR 20BID group, and 0.6% of subjects (13/2357; 0.6 per 100 subject-years) in the APR 30 BID group Based on EAIR per 100 subject-years in the Apremilast Data Pool, comparable results were observed between apremilast and placebo in adjudicated events of MACE and potential MACE. No dose effect was observed.

Most cases of MACE were classified as myocardial infarction. Most cases of potential MACE were classified as unstable angina requiring hospitalization and/or coronary revascularization procedure. The reported incidence of MACE was comparable with the background epidemiologic data.

Nearly all subjects adjudicated with MACE or potential MACE had two or more major risk factors (e.g., elderly age, hypertension, hyperlipidemia, obesity, and/or type 2 diabetes mellitus) and additional confounding comorbidities (e.g., coronary artery disease and atherosclerosis) that confound an assessment of causality.

Overall, the incidence of MACE or potential MACE in apremilast clinical studies was lower than the background rates for similar populations:

- The rate of adjudicated MACE in apremilast-exposed subjects was in the lower range of the MACE rate in the meta-analysis of psoriasis patients conducted by Ryan et al and was lower than the average from all the IL-12/23 studies analyzed (Ryan, 2011).
- The rate of adjudicated MACE in the apremilast-exposed subjects was lower than that in psoriatic arthritis patients in the CPRD or the MarketScan databases.

Other Cardiac Disorders

Cardiac Failure

In the Apremilast Data Pool, during the Placebo-controlled Period, SMQ cardiac failure TEAEs were reported for 1 (0.1%) subject in the placebo group, 2 (0.2%) subjects in the APR 20 BID group, and 3 (0.2%) subjects in the APR 30 BID group. Two additional subjects (APR 20 BID, 1 subject; APR 30 BID, 1 subject) reported SMQ cardiac failure TEAEs during the Apremilast-exposure Period.

SMQ cardiac failure TEAEs were reported as serious in 4 subjects, 3 subjects with PT cardiac failure congestive (Placebo, 1 [0.1%] subject; APR 20 BID, 2 [0.1%] subjects) and 1 subject with PT cardiac failure (APR 30 BID [< 0.1%]).

Based on EAIR per 100 subject-years there was no evidence of an increased incidence of SMQ cardiac failure TEAEs with longer exposure to apremilast in the Apremilast Data Pool (0.2 and 0.5 per 100 subject-years for the Apremilast-exposure Period and the Treatment Duration Period Weeks 0 to 16, respectively, in the APR Total group).

Tachyarrhythmia

- Apremilast Data Pool

In the Apremilast Data Pool, during the Placebo-controlled Period, events of SMQ tachyarrhythmia TEAEs were reported for 0.2% of subjects in the placebo group, 0.6% of subjects in the APR 20 BID group, and 0.6% of subjects in the APR 30 BID group. The most frequently reported tachyarrhythmia event was atrial fibrillation. Based on EAIR per 100 subject-years, there was no evidence of an increased incidence of SMQ tachyarrhythmia TEAEs with longer exposure to apremilast in the Apremilast Data Pool (1.1 and 1.6 per 100 subject-years for the Apremilast-exposure Period and the Placebo-controlled Period, respectively, in the APR Total group). The majority of the subjects with SMQ tachyarrhythmia TEAEs had an underlying medical history of cardiac disorder or baseline ECG abnormalities. Three subjects discontinued treatment due to these events and 1 subject required dose reduction (Table 71).

Table 71: Apremilast Data Pool: SMQ Analysis of Tachyarrhythmia During the Apremilast-exposure Period (Apremilast Subjects as Treated)

SMQ[a] Preferred Term	APR 20 BID (N=1450) SY=1185.3		APR 30 BID (N=2357) SY=2241.5		APR Total[b] (N=4089) SY=3541.0	
	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Tachyarrhythmia	13 (0.9)	1.1	26 (1.1)	1.2	39 (1.0)	1.1
Atrial fibrillation	7 (0.5)	0.6	8 (0.3)	0.4	15 (0.4)	0.4
Ventricular extrasystoles	2 (0.1)	0.2	5 (0.2)	0.2	7 (0.2)	0.2
Sinus tachycardia	1 (0.1)	0.1	4 (0.2)	0.2	5 (0.1)	0.1
Supraventricular extrasystoles	2 (0.1)	0.2	2 (0.1)	0.1	4 (0.1)	0.1
Atrial flutter	0	0	3 (0.1)	0.1	3 (0.1)	0.1
Supraventricular tachycardia	2 (0.1)	0.2	1 (<=0.1)	0.0	3 (0.1)	0.1
Extrasystoles	0	0	2 (0.1)	0.1	2 (<=0.1)	0.1
Atrial tachycardia	0	0	1 (<=0.1)	0.0	1 (<=0.1)	0.0
Cardiac flutter	0	0	1 (<=0.1)	0.0	1 (<=0.1)	0.0

APR 10/20/30 BID = apremilast 10/20/30 mg twice daily; APR 20/40 QD = apremilast 20/40 mg once daily; SMQ = Standardized MedDRA query; SY = subject-years; TEAE = treatment-emergent adverse event.
a SMQ preferred terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0 and are listed in descending order of subject incidence of the APR Total column.
b The APR Total group includes all apremilast treatment groups (APR 10 BID, APR 20 QD, APR 20 BID, APR 40 QD, and APR 30 BID).
Note: Apremilast exposure includes all data while subjects were exposed to apremilast regardless of when the apremilast exposure started.
A TEAE is an adverse event with a start date on or after the date of the first dose of apremilast and no later than 28 days after the last dose of apremilast. In studies PSOR-008 and PSOR-009, adverse events that started 28 days after initiating placebo and before resuming apremilast treatment in the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) were excluded. Duration of placebo treatment in the withdrawal phase was excluded from apremilast exposure. Each subject was counted once for each applicable category.
Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

Adjudicated Evaluation of Malignancies

Treatment-emergent malignancies were adjudicated and classified as hematologic, skin (excluding melanoma), or solid (including melanoma) malignancies.

- Apremilast Data Pool

Events from 7 (0.5%) subjects in the placebo group, 16 (1.1%) subjects in the APR 20 BID group, and 29 (1.2%) subjects in the APR 30 BID group were identified for adjudication of malignancies; all events except those from 2 APR 20 BID subjects and 1 APR 30 BID subject were evaluable 3 subjects with events that were adjudicated as not evaluable for malignancy events either did not have a biopsy performed or based on the clinical presentation a malignancy cannot be confirmed (data on file).

One event was adjudicated as hematologic malignancy in 1/1450 (0.1%) subjects in the APR 20 BID group.

Events were adjudicated as malignancy of the skin (excluding melanoma) in 0.3% of subjects (4/1411; 0.9 per 100 subject-years) in the placebo group, 0.3% of subjects (5/1450; 0.4 per 100 subject-years) in the APR 20 BID group, and 0.8% of subjects (18/2357; 0.8 per 100 subject-years) in the APR 30 BID group. Events were adjudicated as solid malignancies (including melanoma) 0.1% of subjects (2/1411; 0.5 per 100 subject-years) in the placebo group, 0.3% of subjects (5/1450; 0.4 per 100 subject years) in the APR 20 BID group, and 0.3% of subjects (8/2357; 0.4 per 100 subject-years) in the APR 30 BID group.

Many of the subjects who had events adjudicated as malignancies had a history of risk factors such as a family history, history of previous skin cancer, or exposure to agents known to be associated with increased risk of cancer. In addition, most of these events were diagnosed in the first 6 months of starting treatment with study medication. Based on these findings, it is unlikely that there is causal relationship between apremilast treatment and the events adjudicated as malignancies.

All except 3 subjects (with non-melanoma skin cancer) adjudicated with malignancy events had one or more predisposing risk factors that confound an assessment of causality.

Adjudicated Evaluation of Serious Infections

The adjudicator classified the events into 4 categories: non-opportunistic non-serious infection, non-opportunistic serious infection, non systemic opportunistic infection, and systemic opportunistic infection.

- Apremilast Data Pool

All 38 events sent for adjudication were evaluable. One event (urinary tract infection) was adjudicated as non-opportunistic non-serious infection in 1/1450 (0.1%) subject in the PsA Phase 3 Data Pool; this event was reported as an SAE by the investigator and therefore sent for adjudication.

Events were adjudicated as non-opportunistic serious infections in 0.3% of subjects (4/1411; 0.9 per 100 subject-years) in the placebo group, 0.5% of subjects (7/1450; 0.6 per 100 subject years) in the APR 20 BID group, and 0.8% of subjects (20/2357; 0.9 per 100 subject-years) in the APR 30 BID group. Events were adjudicated as non-systemic opportunistic infections in 0% of subjects (0/1411) subjects in the placebo group, 0.1% of subjects (1/1450; 0.1 per 100 subject-years) in the APR 20 BID group, and 0.1% of subjects (2/2357; 0.1 per 100 subject-years) in the APR 30 BID group. Events were adjudicated as systemic opportunistic infections in 0.1% of subjects (1/1411; 0.2 per 100 subject-years) in the placebo group, 0.1% of subjects (1/1450; 0.1 per 100 subject-years) in the APR 20 BID group, and < 0.1% of subjects (1/2357; 0.0 per 100 subject-years) subjects in the APR 30 BID group.

In the Apremilast Data Pool, the EAIR per 100 subject-years was comparable for apremilast and placebo treated subjects for adjudicated events of opportunistic (systemic and non-systemic) infections. The rate of non-opportunistic serious infections was low (EAIR per 100 subject-years of 0.9 in both the placebo and APR 30 BID groups, and 0.6 per 100 subject-years in the APR 20 BID group) with no specific organism or organ involvement.

The reported incidence of systemic opportunistic infections is comparable with the background epidemiologic data. Based on a review of current clinical safety data, there is no evidence of an increased risk of serious infections (including opportunistic infections) associated with the use of apremilast. In clinical trials, the EAIR per 100 subject-years of adjudicated serious infections (including opportunistic infections) between placebo and apremilast were comparable, indicating no increased risk of serious infections (including opportunistic infections) with apremilast compared with placebo. In addition, based on a review of the published literature, apremilast did not increase the risk of serious infections (including opportunistic infections) compared with background rates.

Tuberculosis

In addition to the adjudicated serious infections discussed, any reported cases or subjects with medical history related to TB were analyzed. In the PsA and PSOR Phase 3 studies, there was no requirement for latent TB screening prior to enrollment; it was left to the investigator's discretion whether or not to test for latent TB. A chest radiograph and medical history were assessed as part of study screening. Subjects with active TB or a history of incompletely treated TB were excluded from participation. There were no cases of TB reactivation in the PsA Phase 3 Data Pool, PSOR Phase 3 Data Pool, or Apremilast Data Pool. A positive skin test without confirmation of active TB was reported in 3 subjects with no reported medical history of TB.

- PsA Phase 3 Data Pool

In the PsA Phase 3 Data Pool, there were 20 (1.0%) subjects (1.0% in the placebo group, 0.7% in the APR 20 BID group, and 1.2% in the APR 30 BID group) with a medical history of TB (including latent TB, pulmonary TB, and disseminated TB). In addition, 12 (0.6%) subjects had a medical history of a positive tuberculin test: 0.6% in the placebo group, 0.7% in the APR 20 BID group, and 0.4% in the APR 30 BID group).

There were no cases of TB reactivation reported in the PsA Phase 3 Data Pool.

- PSOR Phase 3 Data Pool

In the PSOR Phase 3 Data Pool, there were 7 (0.6%) subjects (0.5% in the placebo group and 0.6% in the APR 30 BID group) with a medical history of TB (including latent TB, pulmonary TB, and disseminated TB). In addition, 2 (0.5%) subjects, both in the placebo group, had a medical history of a positive tuberculin test.

There were no cases of TB reactivation reported in the PSOR Phase 3 Data Pool.

However, 2 subjects in Study PSOR-008 had a positive QuantiFERON®-TB Gold Test during the study. These cases were sent for adjudication and 1 was adjudicated as latent TB. It is unknown whether the subject had latent TB prior to study enrollment as no prior skin test was required. The subject discontinued the study for other reasons. For the second case, the adjudicator's diagnosis was "Fever of unclear origin; unspecified bacterial infection". The subject was discontinued from the study and treated with TB therapy without confirmation of active TB.

Psychiatric Events

Suicidal Ideation and Behaviour

An analysis of treatment-emergent suicidal ideation and behaviour was conducted based on a search using the narrow SMQ terms of suicide and self-injury. In the Apremilast Data Pool, there were 5 subjects with SMQ suicide and self-injury TEAEs during the Placebo-controlled Period, 1 (0.1%) subject in the placebo group, 2 (0.2%) subjects in the APR 20 BID group, and 2 (0.1%) subjects in the APR 30 BID group. Two (0.1%) subjects reported suicidal ideation and 2 (0.1%) subjects reported suicide attempt in the apremilast groups (APR Total), and 1 (0.1%) subject completed suicide in the placebo group.

Depression

An analysis of treatment-emergent depression was conducted based on a search using the narrow SMQ terms. In the Apremilast Data Pool, during the Placebo-controlled Period, the incidence of reports of SMQ depression TEAEs (excluding suicide and self-injury) was higher in the APR 20 BID (1.2%) and APR 30 BID (1.1%) groups than the Placebo (0.6%) group. However, based on EAIR per 100 subject-years there is no evidence that depression is reported at an increased incidence with longer apremilast exposure (2.2

and 3.4 per 100 subject-years for the Apremilast-exposure Period and the Placebo-controlled Period, respectively, in the APR Total group).

Psychiatric Events PSOR Phase 3 Data Pool

In the PSOR Phase 3 Data Pool during the Treatment Duration Period Weeks 0 to 16, the incidence of reports of SMQ depression TEAEs (excluding suicide and self-injury) was higher in the APR 30 BID group (1.2%) than the placebo group (0.5%) (Table 72 & Table 73). However, based on EAIR per 100 subject-years there is no evidence that depression is reported at an increased incidence with longer apremilast exposure (2.2 and 4.2 per 100 subject-years for the Apremilastexposure Period and the Treatment Duration Period Weeks 0 to 16, respectively, for Apremilast Subjects as Treated).

Table 72: PSOR Phase 3 Data Pool: SMQ Analysis of Depression During the Treatment Duration Period Weeks 0 to 16 (Subjects as Treated)

SMQ[a] Preferred Term	Placebo (N=418) SY=116.5		APR 30 BID (N=1184) SY=338.6	
	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Depression (excl suicide and self-injury)	2 (0.5)	1.7	14 (1.2)	4.2
Depression	2 (0.5)	1.7	14 (1.2)	4.2

APR 30 BID = apremilast 30 mg twice daily; PSOR = psoriasis; SMQ = Standardized MedDRA Query; SY = subject-years.
a SMQ preferred terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0 and are listed in descending order of APR 30 BID column.
Note: For Subjects as Treated, data for the first 16 weeks of exposure are included regardless of when apremilast exposure started, ie, for subjects treated with apremilast at Week 0, data from Weeks 0 to 16 are included, whereas for subjects who are first treated with apremilast at Week 16 data from Weeks 16 to 32 are included.
A TEAE is an adverse event with a start date on or after the date of the first dose of investigational product (IP) and no later than 28 days after the last dose of IP. Each subject is counted once for each applicable category.
Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

Table 73: PSOR Phase 3 Data Pool: SMQ Analysis of Depression During the Apremilast-exposure Period (Apremilast Subjects as Treated)

SMQ[a] Preferred Term	APR 30 BID (N=1184) SY=1127.9	
	n (%)	EAIR per 100 SY
Depression (excl suicide and self-injury)	25 (2.1)	2.2
Depression	25 (2.1)	2.2

APR 30 BID = apremilast 30 mg twice daily; PSOR = psoriasis; SMQ = Standardized MedDRA Query; SY = subject-years.
a SMQ preferred terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0 and are listed in descending order of subject incidence.
Note: For Apremilast Subjects as Treated, all data while subjects were exposed to apremilast regardless of when the apremilast exposure started are included.
A TEAE is an adverse event with a start date on or after the date of the first dose of apremilast and no later than 28 days after the last dose of apremilast. Adverse events started 28 days after initiating placebo and before resuming apremilast treatment in the randomized withdrawal phase (Weeks 32 to 52) are excluded. Placebo exposure duration is excluded from apremilast exposure. Each subject is counted once for each applicable category.
Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

- Apremilast Data Pool

In the Apremilast Data Pool, during the Placebo-controlled Period, the incidence of reports of SMQ depression TEAEs (excluding suicide and self-injury) was higher in the APR 20 BID (1.2%) and APR 30 BID (1.1%) groups than the Placebo (0.6%) group (Table 74). However, based on EAIR per 100 subject-years there is no evidence that depression is reported at an increased incidence with longer apremilast exposure (2.2 and 3.4 per 100 subject-years for theApremilast-exposure Period and the Placebo-controlled Period, respectively, in the APR Total group).

Table 74: Apremilast Data Pool: SMQ Analysis of Depression During the Placebo controlled Period (Subjects as Initially Treated at Week 0)

SMQ[a] Preferred Term	Placebo (N=1411) SY=429.5		APR 20 BID (N=999) SY=377.4		APR 30 BID (N=1668) SY=574.5		APR Total[b] (N=2910) SY=1010.0	
	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY	n (%)	EAIR per 100 SY
Depression (excl suicide and self-injury)	8 (0.6)	1.9	12 (1.2)	3.2	19 (1.1)	3.3	34 (1.2)	3.4
Depression	8 (0.6)	1.9	10 (1.0)	2.7	18 (1.1)	3.2	29 (1.0)	2.9
Depressed mood	0	0	2 (0.2)	0.5	1 (0.1)	0.2	4 (0.1)	0.4
Dysthymic disorder[c]	0	0	0	0	0	0	1 (<0.1)	0.1

APR 10/20/30 BID = apremilast 10/20/30 mg twice daily; APR 20/40 QD = apremilast 20/40 mg once daily; excl = excluding; SMQ = Standardized MedDRA query; SY = subject-years; TEAE = treatment-emergent adverse event.
a SMQ preferred terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0 and are listed in descending order of subject incidence of the APR Total column.
b The APR Total group includes all apremilast treatment groups (APR 10 BID, APR 20 QD, APR 20 BID, APR 40 QD, and APR 30 BID).
c One TEAE of dysthymic disorder was reported in a subject in the APR 10 BID group.
Note: Placebo-controlled Period includes data during the Placebo-controlled Period of each study. In PSA-002, PSA-003, PSA-004, PSA-005, and RA-002 only data up to Week 16 were included for placebo-treated subjects who escaped early, whereas data up to Week 24 were included for apremilast-treated subjects in these studies.
A TEAE is an adverse event with a start date on or after the date of the first dose of investigational product (IP) and no later than 28 days after the last dose of IP. Each subject was counted once for each applicable category.
Exposure-adjusted incidence rate (EAIR) per 100 subject-years is 100 times the number (n) of subjects reporting the event divided by subject-years (up to the first event start date for subjects reporting the event).

Vasculitis

An analysis of vasculitis was conducted based on a search using the narrow SMQ terms listed.

Three subjects in the Apremilast Data Pool had confirmed TEAEs of cutaneous vasculitis, 1 (0.1%) subject in the placebo group (rheumatoid arthritis) and 2 (0.1%) subjects receiving APR30 BID (1 subject, psoriatic arthritis; 1 subject, rheumatoid arthritis). In addition, there was 1 subject with a TEAE of polymyalgia rheumatica in the APR 40 QD group in Phase 2 Study PSA-001 that was non-serious and was not regarded as a case of vasculitis.

In non-clinical toxicology studies in mice, apremilast-related vascular and perivascular inflammation and necrosis with resultant hemorrhage (skeletal muscle, abdominal wall, mesentery, mammary gland and adjacent musculature) and hepatic infarction was observed. This finding was not observed in other species. As a result of the findings in mice, a proinflammatory panel that included antinuclear antibody (ANA) and serum antineutrophilic cytoplasmic antibody (ANCA) was routinely measured at baseline, Weeks 4, 8, and 12 in Phase 2 Study PSOR-003. In this study, there were no differences between treatment groups in the number of subjects with improvement or worsening of ANA titers at the end of the treatment phase. None of the mean changes in the proinflammatory syndrome biomarker panel were considered to be clinically relevant, and no subject exhibited any clinical signs or symptoms of a proinflammatory syndrome. In addition, there were no notable findings in the immunology parameters. Furthermore, there were no notable changes in clinical laboratory tests or peripheral blood markers of inflammation (white blood cell [WBC] or neutrophil counts, erythrocyte sedimentation rate [ESR], albumin, fibrinogen, or C-reactive protein [CRP]) monitored in the Phase 2 clinical studies.

Hypersensitivity Adverse Events

An analysis of treatment-emergent hypersensitivity was conducted based on a search using the SCQ terms listed. The discussion of hypersensitivity in this section focuses on the Apremilast Data Pool. In the data set analyzed, one apremilast-treated subject experienced hypersensitivity with two positive rechallenges leading to drug discontinuation. Another 17 apremilast-treated subjects who experienced hypersensitivity continued apremilast treatment. None of the hypersensitivity reactions were severe and

none led to drug withdrawal, except for the 1 case described above. In the proposed labelling, apremilast is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients.

In the Apremilast Data Pool, during the Placebo-controlled Period, SCQ hypersensitivity TEAEs were reported for 0.1% of subjects in the placebo group, 0.4% of subject in the APR 20 BID group, and 0.3% of subjects in the APR 30 BID group. The EAIR per 100 subject-years was 0.5 and 1.0 per 100 subject-years for the Apremilast-exposure Period and the Placebo-controlled Period, respectively, in the APR Total group.

Overall, SCQ hypersensitivity TEAEs were reported in 19 subjects: 17 subjects treated with apremilast, 1 subject who received placebo and 1 subject who had 2 hypersensitivity reactions (one while receiving placebo and one while receiving apremilast). Of the 18 subjects who received apremilast and experienced hypersensitivity, 16 had an alternative etiology, such as environmental or animal allergy, or hypersensitivity to non-study medication.

One subject receiving APR 10 BID in a Phase 2 psoriasis study was reported as having an anaphylactic reaction on Day 136 that dose change. One subject receiving APR 40 QD in a Phase 2 psoriatic arthritis study

One subject had drug interrupted and ultimately discontinued due to repeated hypersensitivity reactions. The subject had the first reaction (throat tightness, pruritus, and urticaria) on Study Day 27 that resolved on Study Day 29. This subject was rechallenged twice with apremilast and had similar reactions (urticaria, skin welts, pruritus, throat tightness and rash). The subject's medical history included asthma, drug intolerance to sulfa products, and hypersensitivity to penicillin. The subject discontinued apremilast and recovered.

All other subjects continued their study medication after the hypersensitivity event, with no additional events. None of the hypersensitivity events reported in the Apremilast Data Pool was reported as serious.

Weight Change

In an analysis of weight measurement, moderate observed weight loss (>5%) occurred in a higher percentage of subjects who received apremilast than subjects who received placebo. In the Apremilast Data Pool, mean weight change from baseline in the placebo group was +0.11 kg at Week 16. Mean weight change from baseline at Week 16 was -0.88 kg in the APR 20 BID group and -1.24 kg in the APR 30 BID group, and mean weight change from baseline at Week 52 was -1.32 kg in the APR 20 BID group and -1.86 kg in the APR 30 BIDgroup. In the PsA Phase 3 Data Pool, where there was a direct comparison between APR 20 BID and APR 30 BID, the observed weight loss in subjects treated with APR 30 BID was greater than that in subjects treated with APR 20 BID. For the majority of subjects, observed weight loss (> 5%) occurred after the first 16 weeks of treatment, while the majority of nausea and diarrhoea events tended to occur early and resolve within 4 weeks (Table 75).

Table 75: Apremilast Data Pool: Summary of Weight Percent Change From Baseline at the End of Period During the Apremilast-exposure Period (Apremilast Subjects as Treated)

Weight % Change Category	APR 20 BID n (%)	APR 30 BID n (%)	APR Total n (%)
Overall	m[a] = 1373	m[a] = 2268	m[a] = 3606
< -20%	2 (0.1)	11 (0.5)	14 (0.4)
≥ -20% to < -10%	53 (3.9)	101 (4.5)	157 (4.0)
≥ -10% to < -5%	144 (10.5)	311 (13.7)	466 (11.9)
≥ -5% to < 0%	565 (41.2)	923 (40.7)	1602 (41.0)
0%	125 (9.1)	162 (7.1)	325 (8.3)
> 0% to ≤ 5%	410 (29.9)	610 (26.9)	1109 (28.4)
> 5% to ≤ 10%	56 (4.1)	116 (5.1)	179 (4.6)
> 10% to ≤ 20%	18 (1.3)	29 (1.3)	48 (1.2)
> 20%	0	5 (0.2)	6 (0.2)

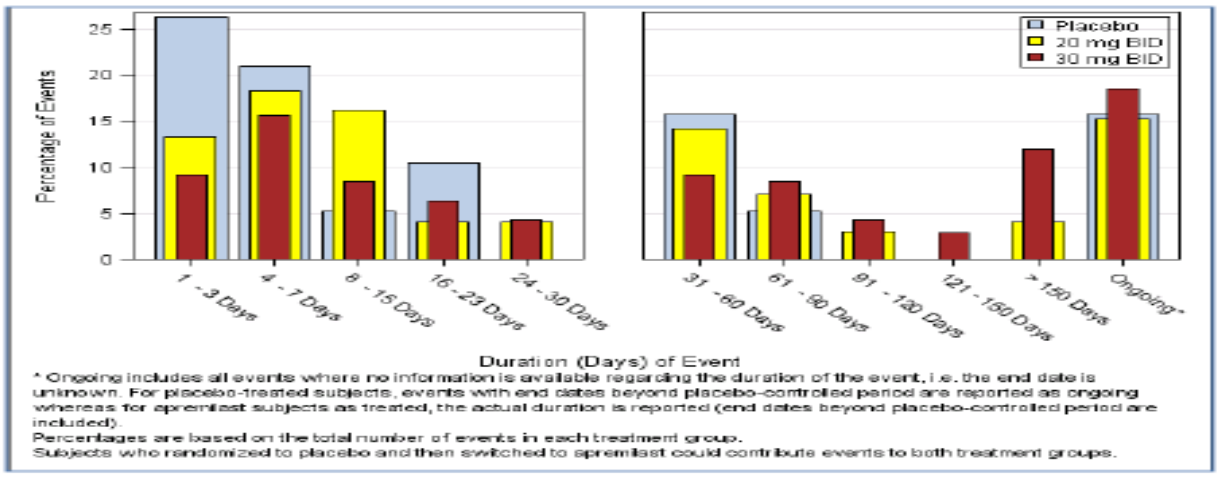
APR 20/30 BID = apremilast 20/30 mg twice daily.
a m = number of subjects with a baseline value and at least 1 postbaseline value; percentages are based on m.
Note: Apremilast exposure includes all data while subjects were exposed to apremilast regardless of when the apremilast exposure started. In studies PSOR-008 and PSOR-009, data collected in the randomized withdrawal phase (Weeks 32 to 52) 28 days after initiating placebo and before resuming apremilast are excluded. Duration of placebo treatment in the withdrawal phase is excluded from apremilast exposure.
The end-of-period value is the last postbaseline value (while subjects were receiving apremilast), including data up to 28 days after the last dose of apremilast but excluding the observational follow-up visit.

Gastrointestinal Events

Analyses of treatment-emergent diarrhoea and GI pain and abdominal pain were conducted based on a search using SCQ terms. Detailed analyses of the duration, onset, and severity of diarrhoea (PT) and nausea (PT) during the Treatment Duration Period Weeks 0 to 16 in the PsA Phase 3 and PSOR Phase 3 Data Pools are also presented in this section.

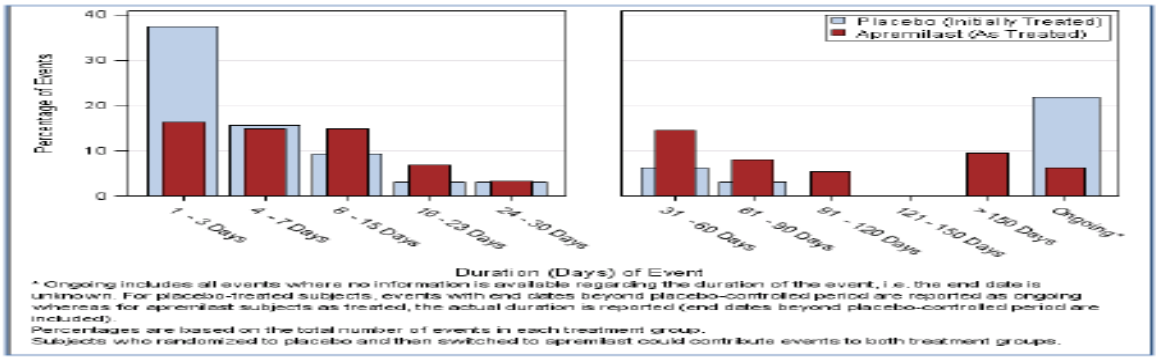
Gastrointestinal events, including diarrhoea, nausea, and abdominal pain werre reported as commonly associated with the use of other PDE4 inhibitors. The data showed that these events are also associated with apremilast treatment, with a dose-related effect observed both for subject incidence of TEAEs as well as withdrawal of study drug due to TEAEs. Most TEAEs of diarrhoea and nausea, the most frequently reported GI events, were mild or moderate in severity and infrequently (< 2% of subjects) led to discontinuation of the study drug. Few TEAEs were reported as serious (1 APR subject for both diarrhoea and nausea), with no apparent treatment- or dose-related effects. During the Treatment Duration Period Weeks 0 to 16, most TEAEs of diarrhoea and nausea occurred within the first 2 weeks of treatment and resolved within 4 weeks of onset.

Figure 13 - PsA Phase 3 Data Pool: Treatment-emergent Diarrhoea Events by Duration of Event Category During the Treatment Duration Period Weeks 0 to 16 (Subjects as Treated)



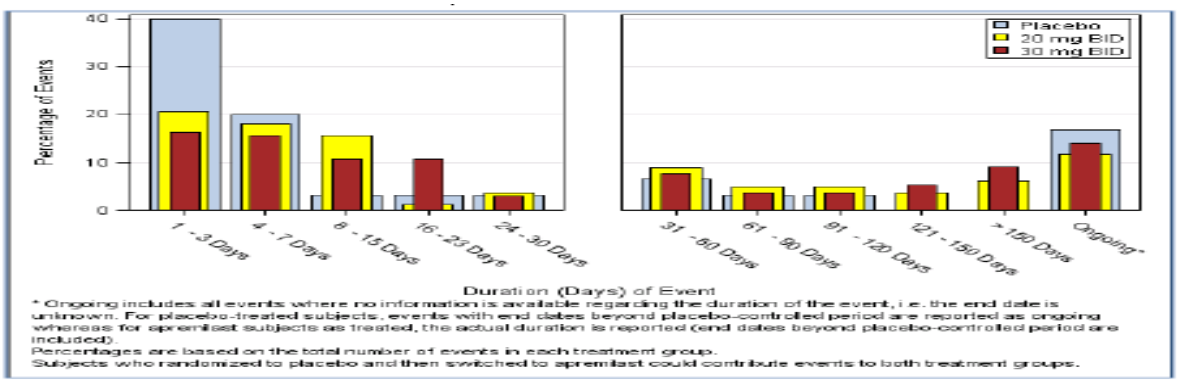
APR 20/30 BID = apremilast 20/30 mg twice daily; PsA = psoriatic arthritis; TEAE = treatment-emergent adverse event.
Total number of events: Placebo, 19; APR 20 BID, 98; APR 30 BID, 140
Note: Duration of each report of the event is the interval between the onset day and the reported TEAE end date. For placebo-treated subjects, TEAEs with end dates beyond Week 16 are reported as ongoing, while for Apremilast Subjects as Treated, end dates beyond Week 16 are included.

Figure 14 - PSOR Phase 3 Data Pool: Treatment-emergent Diarrhoea Events by Duration of Event Category During the Treatment Duration Period Weeks 0 to 16 (Subjects as Treated)



APR 30 BID = apremilast 30 mg twice daily; PSOR = psoriasis; TEAE = treatment-emergent adverse event.
Total number of events: Placebo, 32; APR 30 BID, 221.
Duration of each report of the event is the interval between the onset day and the reported TEAE end date. For placebo-treated subjects, TEAEs with end dates beyond Week 16 are reported as ongoing, while for Apremilast Subjects as Treated, end dates beyond Week 16 are included.

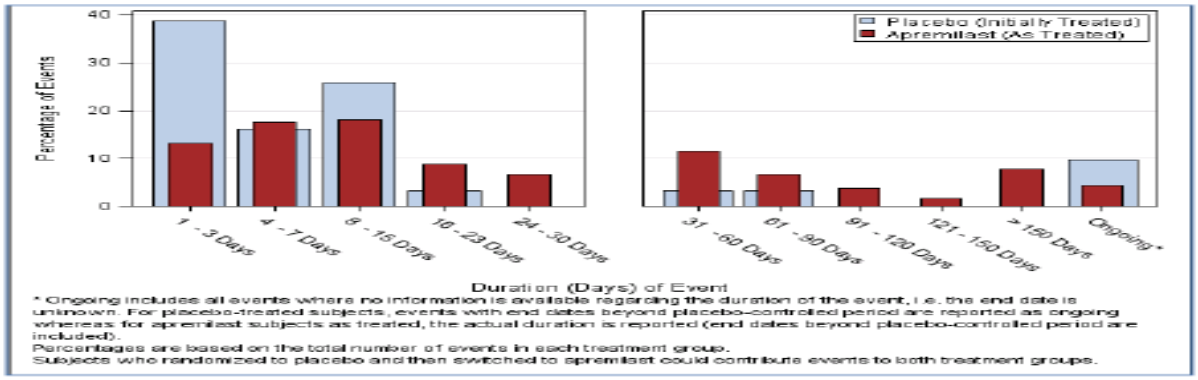
Figure 15 - Treatment-emergent Nausea Events by Duration of Event Category During the Treatment Duration Period Weeks 0 to 16 (Subjects as Treated PsA datapool)



* Ongoing includes all events where no information is available regarding the duration of the event, i.e. the end date is unknown. For placebo-treated subjects, events with end dates beyond placebo-controlled period are reported as ongoing whereas for apremilast subjects as treated, the actual duration is reported (end dates beyond placebo-controlled period are included).
Percentages are based on the total number of events in each treatment group.
Subjects who randomized to placebo and then switched to apremilast could contribute events to both treatment groups.

APR 20/30 BID = apremilast 20/30 mg twice daily; PsA = psoriatic arthritis; TEAE = treatment-emergent adverse event.
Total number of events: Placebo, 30; APR 20 BID, 78; APR 30 BID, 130.
Note: Duration of each report of the event is the interval between the onset day and the reported TEAE end date. For placebo-treated subjects, TEAEs with end dates beyond Week 16 are reported as ongoing, while for Apremilast Subjects as Treated, end dates beyond Week 16 are included.

Figure 16 - PSOR Phase 3 Data Pool: Treatment-emergent Nausea Events by Duration of Event Category During the Treatment Duration Period Weeks 0 to 16 (Subjects as Treated)



* Ongoing includes all events where no information is available regarding the duration of the event, i.e. the end date is unknown. For placebo-treated subjects, events with end dates beyond placebo-controlled period are reported as ongoing whereas for apremilast subjects as treated, the actual duration is reported (end dates beyond placebo-controlled period are included).
Percentages are based on the total number of events in each treatment group.
Subjects who randomized to placebo and then switched to apremilast could contribute events to both treatment groups.

APR 30 BID = apremilast 30 mg twice daily; PSOR = psoriasis; TEAE = treatment-emergent adverse event.
Total number of events: Placebo, 31; APR 30 BID, 182.
Duration of each report of the event is the interval between the onset day and the reported TEAE end date. For placebo-treated subjects, TEAEs with end dates beyond Week 16 are reported as ongoing, while for Apremilast Subjects as Treated, end dates beyond Week 16 are included.

Headache and Tension Headache

An analysis of treatment-emergent headache and tension headache was conducted based on a search using SCQ terms listed. In order to appropriately assess the rate of headache in the apremilast program, TEAEs of tension headache and headache were combined in the SCQ evaluation of headache. The data showed that headache is associated with apremilast treatment, with a dose-related effect observed both for subject incidence of TEAEs as well as withdrawal of study drug due to TEAEs. Most SCQ headache TEAEs were mild or moderate in severity and few were reported as serious, with no apparent treatment- or dose-related effects. During the Treatment Duration Period Weeks 0 to 16, most SCQ headache TEAEs occurred within the first 2 weeks of treatment and resolved within 4 weeks of onset.

Laboratory findings

Clinical Laboratory Parameters, Vital Signs, and Electrocardiograms

Routine laboratory monitoring included assessment of haematology and clinical chemistry parameters. Markedly abnormal laboratory test results were infrequent and transient. There were no cases of LFT elevations meeting Hy's Law criteria. There was no imbalance in renal or other laboratory parameters. There was no evidence of myelosuppression with apremilast treatment.

Based on the results from the PsA Phase 3 Data Pool, mean vital signs assessments (systolic and diastolic blood pressure and pulse rate) did not change throughout the Placebo-controlled Period and the Apremilast-exposure Period.

Based on the results from the thorough QTc study (Study CC-10004-PK-008) and the PsA Phase 3 Data Pool, the use of apremilast did not have any clinically meaningful impact on the QTc interval. Electrocardiogram monitoring with the use of apremilast is not considered necessary.

Safety in special populations

Age

With regard to effects of treatment on age, the incidence of serious TEAEs and TEAEs leading to drug withdrawal was higher in subjects ≥65 years of age compared with those <65 years of age in all treatment groups. The difference between age groups was more pronounced in apremilast-treated subjects than placebo subjects, with a trend suggesting a dose effect. The difference between age groups was driven by GI TEAEs. There was no consistent effect of age on other frequently reported TEAEs.

Sex

A higher incidence of TEAEs, serious TEAEs, and TEAEs leading to drug withdrawal was observed among female subjects compared with male subjects across all treatment groups. The results of a PK study in healthy subjects demonstrated a modestly increased overall exposure in elderly subjects by about 14% and in female subjects by about 30% compared with young and male subjects, respectively.

Race

The numbers of non-white subject in the data pools were too small for a meaningful analysis of TEAEs by race. Similarly, the numbers of Hispanic or Latino subjects were too small for a meaningful analysis of TEAEs by ethnicity. The results of a PK study (CC-10004-CP-018) in healthy male Japanese, Chinese, and Caucasian (white) subjects demonstrated comparable apremilast exposure between Japanese and white subjects and between Chinese and white subjects.

Subjects With Renal Impairment

In patients with severe renal impairment single-dose oral administration of 30 mg of apremilast resulted in an increase in overall mean exposure (AUC0–∞) by 88.5% relative to demographically matched healthy subjects. These changes in overall exposure did not correlate with the AEs observed in this single-dose study. The effect of mild and moderate renal impairment on apremilast PK was not directly assessed. However, population PK analyses in 54 subjects with RA or PsA, who had mild or moderate renal impairment, did not find a correlation between creatinine clearance (CLcr) and apremilast clearance. The apremilast exposure in RA or PsA subjects with mild or moderate renal impairment was similar to RA or PsA subjects with normal renal function.

Subjects With Hepatic Impairment

In Study CC-10004-CP-011, PK parameters calculated for the moderately hepatic-impaired group (following a 30-mg single dose of apremilast) and severely hepatic-impaired group (following a 20-mg single dose of apremilast) and demographically matched healthy groups were comparable with each other. A majority of the AEs observed were associated with patients with severe hepatic impairment and were likely due to their underlying disease conditions.

Use in Pregnancy and Lactation

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. Apremilast was detected in milk of lactating mice. A risk to the breastfed infant cannot be excluded, therefore apremilast should not be used during breast-feeding.

Pregnant and lactating women were excluded from the study population and throughout the clinical development program. Women of childbearing potential were required to use protocol approved, effective means of contraception for the duration of their participation in apremilast trials and for at least 28 days thereafter. Similarly, male study subjects who engaged in sexual activity from which conception was possible were also required to use condoms for the duration of their participation in apremilast trials and for at least 28 days thereafter.

As of 15 May 2013, there were 21 pregnancies (7 female subjects and 14 partners of male subjects) reported during the apremilast clinical trials. Of the 7 female subjects, 2 were either on placebo or the pregnancy occurred during pretreatment, and 5 occurred while receiving apremilast. Of the 14 male subjects, 3 were either on placebo or the partner pregnancy was reported to have occurred during pretreatment and 11 were on apremilast.

Female Subjects: Pregnancy Outcomes

There were no congenital anomalies reported for any subject who became pregnant while being exposed to apremilast/blinded therapy. The elective terminations had no pathology reports. No spontaneous abortions were reported in female subjects receiving active apremilast treatment.

The 2 live births reported to date with female subjects exposed to apremilast therapy were fullterm healthy babies.

Partners of Male Subjects: Pregnancy Outcomes

There were no congenital anomalies reported for partners of male subjects who became pregnant or were pregnant while their partners were exposed to apremilast/blinded therapy. There were 2 spontaneous abortions in partners of male subjects who became pregnant or were pregnant while their partners were exposed to apremilast therapy. Live births (9)reported to date in partners of male subjects exposed to apremilast therapy were full-term healthy babies

Age

The incidence of ADRs was comparable for subjects < 65 and 65 to74 years of age. The numbers of subjects 75 to 84 years of age and ≥ 85 years of age were too small to make meaningful conclusions.

Table 2: **Table 3: Adverse Drug Reactions by Age Category – Apremilast Exposure Period – Apremilast Total (Subjects as Treated)**

MedDRA Terms	Age < 65 N = 3684 n (%)[a]	Age 65-74 N = 361 n (%)[a]	Age 75-84 N = 43 n (%)[a]	Age 85+ N = 1 n (%)[a]
Total ADRs	**1853 (50.3)**	**168 (46.5)**	**23 (53.5)**	**0**
Serious ADRs – Total	**9 (0.2)**	**1 (0.3)**	**0**	**0**
Fatal	0	0	0	0
Hospitalization/prolong existing hospitalization	6 (0.2)	1 (0.3)	0	0
Life-threatening	0	0	0	0
Disability/incapacity	0	0	0	0
Other (medically significant)	2 (0.5)	0	0	0
ADRs leading to drop-out	137 (3.7)	22 (6.1)	5 (11.6)	0
Psychiatric disorders (SOC)	75 (2.0)	11 (3.0)	1 (2.3)	0
Nervous system disorders (SOC)	538 (14.6)	32 (8.9)	6 (14.0)	0
Accidents and injuries (SMQ)	0	0	0	0
Cardiac disorders (SOC)	0	0	0	0
Vascular disorders (SOC)	0	0	0	0
Cerebrovascular disorders (SMQ)	0	0	0	0
Infections and infestations (SOC)	854 (23.2)	70 (19.4)	4 (9.3)	0
Quality of life decreased (PT)	0	0	0	0

ADR = adverse drug reaction; AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = standardized MedDRA queries; SOC = system organ class
[a] Cumulative number over all indications in the clinical program and percentage over the age group.
Source: Table R.3.6.2, Table R.3.8.2, Table R.3.9.2, Listing L.2.

Safety related to drug-drug interactions and other interactions

Other Drug-drug Interactions

Drug-drug interaction studies were conducted with methotrexate, ketoconazole, rifampicinn, and oral contraceptives (OC) to evaluate the potential effect on the PK of apremilast.

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.

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.

Discontinuation due to adverse events

Treatment-emergent Adverse Events Leading to Drug Withdrawal

PsA Phase 3 Data Pool

- Treatment Duration Period Weeks 0 to 16

Overall, TEAEs leading to drug withdrawal were infrequent, i.e., 3.6% of subjects in the placebo group and 4.9% of subjects as treated in the APR Total group, including 4.5% of subjects receiving APR 20 BID and 5.2% of subjects receiving APR 30 BID. The most frequently reported TEAEs leading to drug withdrawal were diarrhoea (placebo 0.4%,APR 20 BID 1.1%, APR 30 BID 1.7%), nausea (placebo 0.4%, APR 20 BID 1.0%, APR 30 BID 1.5%), and headache (placebo 0.3%, APR 20 BID 0.4%, APR 30 BID 1.2%)

- Apremilast-exposure Period

Overall, TEAEs leading to drug withdrawal occurred in 7.2% of subjects who received apremilast (APR Total group), 6.9% of subjects in the APR 20 BID group and 7.5% of subjects in the APR 30 BID group. During the Apremilast-exposure Period for subjects as treated, the EAIRs per 100 subject-years for TEAEs leading to drug withdrawal were 7.2 in the APR 20 BID group and 7.8 in the APR 30 BID group.

The 3 most frequently reported TEAEs leading to drug withdrawal in the PsA Phase 3 Data Pool during the Apremilast-exposure Period were the same as those reported during the Treatment Duration Periods Weeks 0 to 16, i.e., diarrhoea, nausea, and headache.

PSOR Phase 3 Data Pool

Treatment Duration Period Weeks 0 to 16

Overall, TEAEs leading to drug withdrawal were infrequent, i.e., 3.8% for subjects treated with placebo and 4.8% for the Apremilast Subjects as Treated population with APR 30 BID. The most frequently reported TEAEs leading to drug withdrawal were nausea (placebo 0.2%, Apremilast Subjects as Treated with APR 30 BID 1.2%) and diarrhoea (placebo 0.2%, Apremilast Subjects as Treated with APR 30 BID 0.8%).

- Apremilast-exposure Period

Overall, TEAEs leading to drug withdrawal occurred in 8.4% of subjects who received APR 30 BID. During the Apremilast-exposure Period for the Apremilast Subjects as Treated population, the EAIR per 100 subject-years for TEAEs leading to drug withdrawal was 8.8 in the APR 30 BID group. During the Treatment Duration Period Weeks 0 to 16 for the Apremilast Subjects as Treated population, the EAIR per 100 subject-years for TEAEs leading to drug withdrawal was 17.0 in the APR 30 BID group. Based on EAIR per 100 subject-years, there is no evidence of an increased incidence of TEAEs leading to drug withdrawal with longer exposure to apremilast.

- Apremilast Data Pool

During the Placebo-controlled Period, TEAEs leading to drug withdrawal occurred in 4.5% of subjects in the placebo group and 6.3% of subjects in the APR Total group, including 6.0% of subjects receiving APR 20 BID and 6.4% of subjects receiving APR 30 BID. The most frequently reported TEAEs leading to drug withdrawal during the Placebo-controlled Period were nausea, diarrhoea, and headache. Overall, TEAEs leading to drug withdrawal occurred in 8.1% of subjects in the APR Total group, including 7.7% of subjects receiving APR 20 BID and 8.5% of subjects receiving APR 30 BID. Only nausea and diarrhoea were reported as leading to drug discontinuation in ≥1% of Apremilast Subjects as Treated, with a trend suggesting a dose effect

2.6.1. Discussion on clinical safety

More than 4000 subjects were treated in the clinical development programme. This included subjects treated with moderate to severe psoriasis and subjects with psoriatic arthritis. The applicant presents pooled safety data from all subjects treated for the proposed indications in the phase 2/3 data pool. Within this data pool the applicant presented safety data for each indication, i.e. data from subjects with: Psoriatic arthritis (the PsA Phase 3 Data Pool); Moderate to severe psoriasis treated (the PSOR Phase 3 Data Pool); apremilast datapool in the phase 2/3 development programme comprises all Phase 2/3 clinical studies that evaluated the safety of apremilast in the treatment of psoriasis, psoriatic arthritis, or rheumatoid arthritis. The length of treatment ranged from 29 days (in 1 psoriasis study) to 52 weeks with ongoing studies of up to 5 years exposure. The doses used in the phase 2/3 programme ranged from 20-30mg BID (in 1 study 40mg bd) reflecting the intended dose to be used in both indications. The size of the safety database was considered adequate by the CHMP as was the length of exposure.

The applicant's approach was considered complex by the CHMP but did provide the incidence of adverse events for each indication taking part in the trial compared to placebo. Exposure Adjusted Incidence Rates (EAIR) were used in an attempt to estimate the incidence of these adverse events over time as it is likely that patients will be treated for longer than 16 weeks. The use of exposure adjusted incidence rates assumes that the events occur early and that the occurrence of the adverse event is constant over time. It is not considered suitable for adverse events with a latency period. As the applicant pointed out, the incidence of the gastrointestinal events associated with apremilast may not be constant over time. In addition, malignancies may have a latent period from exposure to presentation. The extension clinical trials as well as the proposed disease registry and data from CPRD will further characterise malignancies and long-term safety as described in the RMP.

The populations in the data pools were balanced across groups, with over 80% of subjects completing the study. The severity of disease, medical history and concomitant medication were also balanced across groups. The mean and median weight and BMI were high across all groups. This reflects the population studied i.e. approximately half of subjects recruited in North America. However posology is not based on weight but subjects are titrated from 10 to 30 mg daily based on tolerability. The CHMP noted a tendency towards an increased incidence of TEAEs and SAEs in subjects with BMI<25mg/m^2. There was no evidence for any difference in the safety profile of apremilast across the subgroups of subjects with baseline BMI <25 mg/m^2, 25 to <30 mg/m^2, and ≥30 mg/m^2. The main reasons for withdrawal were similar in the placebo and active groups. Weight loss of up to 2 kg was also observed in the Apremilast treated group. Weight change has also been described with other PDE4 inhibitors.The applicant has provided an analysis of weight loss in subjects with gastrointestinal symptoms. The majority of those subjects with a weight loss greater than 5% did not experience gastrointestinal symptoms and weight loss occured after 16 weeks treatment whereas gastrointestinal symptoms occurred early in treatment. Gastrointestinal symptoms do not explain the weight loss observed. The CHMP considered that this weight loss could be exacerbated or become clinically significant in subjects with a low BMI who commence treatment or in subjects with persistent diarrhoea or intolerability.The applicant has therefore included the following statement in the product information: "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". Weight decrease in patients with BMI <20 kg/m^2 is also listed in the RMP. Subjects who were treated for 16 weeks had no further weight loss after cessation of treatment.

The majority of subjects were Caucasian however the applicant has completed pharmacokinetic studies in Chinese and Japanese populations which revealed comparable exposures. The number of black subjects was small but balanced across groups. In some groups PK studies indicated increased exposure e.g. the

elderly and in female subjects. During the procedure the applicant has provided analysis showing that although the number of elderly females is relatively small in comparison to the population analysed, and the number of those under 60 kg is even more limited, elderly females should not require lower dosing, even at lower body weights. This was agreed by the CHMP.

Depression is also a significant adverse reaction, which occurred more frequently in the PSOR group than in the placebo group. 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. Depression is included in the product information and in the RMP. This was agreed by the CHMP. The results of the MedDRA SMQ analyses of suicide, suicide attempt, suicidal behaviour, or suicidal ideation could not conclusively demonstrate whether apremilast is causally associated with these events. However the risk of triggering suicide and nervousness are also listed in the RMP.

A total of 7 deaths occurred in the applicant's apremilast clinical development program and 1 death occurred in an investigator-initiated study (in Rheumatoid Arthritis). Of the 7 deaths that occurred in the apremilast clinical studies, 6 deaths occurred in the psoriasis studies (3 subjects treated with APR 30 BID, 1 subject who was initially randomized to apremilast and rerandomized to placebo in the randomized withdrawal period, and 2 subjects treated with placebo) and 1 death occurred in a PsA study (APR 20 BID). The subject who died in the investigator-initiated study was diagnosed with acute myeloid leukemia 8 months after the last dose of study medication. Overall, the number of deaths has been low in the apremilast clinical program. There is no pattern associated with cause of death in apremilast clinical studies.

The percentage of subjects with serious TEAEs in apremilast Phase 2 and Phase 3 clinical studies was low and comparable across treatment groups during the Placebo-controlled Period. The EAIR for SAEs in the APR 20 BID or APR 30 BID groups did not increase during the apremilast-exposure Period; therefore, there is no evidence that the incidence of SAEs increases with longer exposure of apremilast treatment. The incidence of SAEs was not driven by any single preferred term or specific, individual organ toxicity. Cardiac adverse events are a frequent 'other' serious adverse event. The applicant presented an additional evaluation of cardiac events and concluded that based on EAIRs there is no increased risk of cardiac disorder i.e. MACE, tachyarrhythmia or cardiac failure with apremilast exposure. Cardiac safety is also included in the RMP and more information about the risk of MACE will be further evaluated through the PsA and psoriasis disease registry in the EU but also through analysis of relevant data from the CPRD at pre-specified intervals (as described in the RMP).

The percentage of subjects with TEAEs that led to drug withdrawal in apremilast Phase 2 and Phase 3 clinical studies during the Placebo-controlled Period was low. The EAIR for TEAEs that led to drug withdrawal in the APR 20 BID and APR 30 BID groups did not increase during the apremilast-exposure Period; therefore, there is no evidence that the incidence of TEAEs that led to drug withdrawal increases with longer exposure of apremilast treatment. There were no TEAEs leading to discontinuation that occurred in more than 2% of subjects.

Seven subjects in the placebo group versus 45 in the treatment group developed malignancy. Most of the events occurred in the first 6 months. The percentage of total subjects exposed in the trial who developed a malignancy is approximaltely 0.01% which is not greater that the expected background risk. The CHMP concluded that there is no indication that apremilast increases the risk of malignancy from the numbers studied and the length of the clinical trials. The applicant acknowledged that most estimates of malignancy incidence from clinical trials of new therapeutic agents are limited since both the expected numbers of events and the study durations are insufficient to provide a reliable estimate. Data from ongoing long term studies will provide further data (as described in the RMP).

Based on the data provided by the applicant there is no indication of an increased incidence of infections on exposure to apremilast.

The trial population were not screened for latent TB by skin prick test but all subjects had a history taken enquiring about previous infection or positive tests and had a chest x-ray. There was 1 probable case of latent TB out of 4000 subjects. There are no proposals for warnings concerning either serious infections or tuberculosis in the product information as screening for tuberculosis was not required prior to enrolment, and that the clinical trial data have not demonstrated an increased risk of tuberculosis, or serious infections more generally. This was agreed by the CHMP.

Three cases of vasculitis were reported from the apremilast datapool. Two subjects had rheumatoid arthritis and one psoriatic arthropathy. Two subjects were on active treatment and one was on placebo. There were no changes in the proinflammatory panel demonstrated in the phase 2 study PSOR-003. The risk of vasculitis is reflected in the RMP.

The data available regarding exposure in pregnancy is very limited- 11 babies born thusfar. Studies in animals have demonstrated an effect on fetal growth and development. The applicant has updated the product information stating that apremilast is contraindicated in pregnancy. Further information on the potential risks of aprelimast during pregnancy will be provided through the monitoring of planned or unplanned pregnancies exposed to aprelimast in a pregnancy exposure registry in the US and Canada. The final study report from this registry will be provided by the applicant (as described in the RMP). 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. This was agreed by the CHMP.

Subgroup analyses in the PsA Phase 3 Data Pool and the PSOR Phase 3 Data Pool by various intrinsic/extrinsic factors (e.g., age, sex, race, ethnicity, region, medical history, prior biologic use, and concomitant medications) did not identify any safety concerns.

Based on the results of laboratory parameters, vital signs, and ECG, routine monitoring with the use of apremilast is not necessary. There is no evidence of myelosuppression with apremilast treatment. However in subjects with risk factors or whose liver function tests are abnormal treatment with apremilast may raise their LFTs. Apremilast does not prolong the QT interval at the doses of 30 mg and 50 mg BID studied in a dedicated QTc study.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety of apremilast has been well characterized. 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.

The data available regarding exposure in pregnancy is very limited- 11 babies born thusfar. Studies in animals have demonstrated an effect on fetal growth and development. The applicant has updated the product information stating that apremilast is contraindicated in pregnancy. 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.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC Advice.

The applicant implemented the changes in the RMP as requested by PRAC. The CHMP endorsed this advice without changes.

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 76: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Pharmacokinetic interaction with strong CYP3A4 inducers • Weight decrease in patients with BMI < 20 kg/m^2 • Depression
Important potential risks	• Vasculitis • Risk of triggering suicide • Malignancies • Nervousness and anxiety • Serious infections • MACE and tachyarrhythmia • Prenatal embryo-foetal loss and delayed foetal development (reduced ossification and foetal weight) in pregnant women exposed to apremilast

Missing information	• Paediatric use • Patients with moderate and severe renal impairment • Long-term safety • Limited data in long-term efficacy • Patients with moderate and severe hepatic impairment • Use in patients of different racial origin • Live vaccination • Potential pharmacokinetic interactions of apremilast metabolite M12

Pharmacovigilance plan

Table 77: Ongoing and planned studies in the PhV development plan

Study / Activity Type, Title and Category (1 to 3)	**Objectives**	**Safety Concern Addressed**	**Status (planned, started)**	**Date for Submission of Interim or Final Reports (planned or actual)**
Up to 5-year treatment duration of Phase 3 studies(CC-10004-PSA-002, -003, -004, -005 and CC-10004-PSOR-008, -009) to collect long-term data Category 3	To collect long-term data	Malignancies Long-term safety	Ongoing	CSRs anticipated Q4 2017
Up to 2-year treatment duration of Phase 3 study (CC-10004-PSOR-010) to collect long-term data Category 3	To collect long-term data	Malignancies Long-term safety Limited data in long-term efficacy	Ongoing	Interim CSR anticipated Q2 2015 Final CSR anticipated Q3 2016
Apremilast Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Category 3	To monitor planned or unplanned pregnancies exposed to apremilast.	Evaluate whether there is any increase in the risk of birth defects (specifically, a pattern of anomalies) in exposed pregnancies	Ongoing	Final CSR anticipated Jun 2022
Disease Registry in the EU for PsA and psoriasis Category 3	To collect long-term data in real world setting	Hypersensitivity Depression Vasculitis Risk of triggering suicide Malignancies Nervousness and anxiety Serious infections	Planned	The final protocol for the PsoBest registry will be provided by 30 Jun 2015 and the registry will start 01 Jul 2015.

		MACE and tachyarrhythmia Long-term safety		The final protocol for the BSRBR registry will be provided by 31 Dec 2015 and the registry will commence in Jan 2016.
CPRD (UK) data analysis for PsA and psoriasis Category 3	To collect long-term data in real world setting	Hypersensitivity Depression Vasculitis Risk of triggering suicide Malignancies Nervousness and anxiety Serious infections MACE and tachyarrhythmia Long-term safety	Planned	Analysis of the CPRD data at Years 1, 3 and 5, starting from the date of first commercial availability in the UK. A protocol will be submitted for review by 30 Jun 2015. First analysis will be conducted 1 year from the date of first commercial availability in the UK.
In vitro studies (CC-10004-DMPK-1965 and CC-10004-DMPK-1966) Category 3	To evaluate the potential pharmacokinetic interactions of apremilast metabolite M12	Potential pharmacokinetic interactions of apremilast metabolite M12	Ongoing	Final study reports will be submitted Q1 2015

Risk minimisation measures

Table 78: Summary table of Risk Minimisation Measures

Safety Concern	Proposed Routine Risk Minimisation Measures	Proposed Additional Risk Minimisation Measures
Important Identified Risks		
Hypersensitivity	SmPC Contraindicated in patients with hypersensitivity to the active substance or excipients (Section 4.3). Included as an undesirable effect (Section 4.8). PIL Included in the patient information.	None
Pharmacokinetic Interaction with Strong CYP3A4 Inducers	SmPC Includes information on interactions (Sections 4.5 and 5.2). PIL The patient information includes information on interactions.	None
Weight Decrease in Patients with BMI < 20 kg/m^2	SmPC A precaution for underweight patients is included (Section 4.4). Weight decrease is listed as an adverse reaction associated with apremilast (Section 4.8).	None
Depression	SmPC Depression is discussed in Section 4.8.	None
Important Potential Risks		
Vasculitis	Routine risk minimisation activities are not deemed necessary as no specific risk of vasculitis has been detected for apremilast. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance.	None
Risk of Triggering Suicide	Routine risk minimisation activities are not deemed necessary as no specific risk of triggering suicide has been detected for apremilast. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance.	None
Malignancies	Routine risk minimisation activities are not deemed necessary as no specific risk of malignancies has been detected for apremilast. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance.	None
Nervousness and Anxiety	Routine risk minimisation activities are not deemed necessary as no specific risk of nervousness and anxiety has been detected for apremilast. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance.	None

Serious Infections	Routine risk minimisation activities are not deemed necessary as no specific risk of serious infections has been detected for apremilast. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance.	None
MACE and Tachyarrhythmia	Routine risk minimisation activities are not deemed necessary as no specific risk of MACE and tachyarrhythmia has been detected for apremilast. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance.	None
Prenatal Embryo-foetal Loss and Delayed Foetal Development (Reduced Ossification and Foetal Weight) in Pregnant Women Exposed to Apremilast	SmPC Contraindicated in pregnancy (Section 4.3). Includes information regarding use in pregnancy (Section 4.6) and preclinical information on embryo-foetal development (Section 5.3). PIL Includes information regarding use in pregnancy (including do not take if pregnant).	None
Missing information		
Paediatric Use	SmPC Includes information on the use of apremilast in paediatric patients (Section 4.2). PIL The patient information includes a warning that use in children and young people under 17 years is not recommended.	None
Patients with Moderate and Severe Renal Impairment	SmPC Dosage information for patients with renal impairment is provided (Section 4.2).	None
Long-term Safety	SmPC Clinical experience beyond 52 weeks is not available (Section 4.2 and Section 5.1).	None
Limited Data in Long-term Efficacy	SmPC Clinical experience beyond 52 weeks is not available (Section 4.2 and Section 5.1).	None
Patients with Moderate and Severe Hepatic Impairment	SmPC Dosage information for patients with hepatic impairment is provided (Section 5.2).	None
Use in Patients of Different Racial Origin	Routine risk minimisation activities are not deemed necessary as no specific risk in patients of different racial origin has been detected for apremilast. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance.	None
Live Vaccination	Routine risk minimisation activities are not deemed necessary as no specific risk has been detected for apremilast. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance.	None

Potential Pharmacokinetic Interactions of Apremilast Metabolite M12	None	None

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Psoriatic arthritis

A treatment effect in favour of apremilast (mACR primary endpoint 18.3% at week 16 and 15.8% at week 24 $p<0.0001$) was demonstrated for APR30mg BID across the three studies in patients who have previously failed or have not responded to prior DMARD therapy in terms of treatment of symptoms and clinical indices of articular disease activity both for those on DMARDs (small molecule and biological) and for those not on DMARDs at baseline. Improvement in the signs and symptoms of PsA, as measured by the modified ACR 20 response at week 16, continued up to Week 52 across all three pivotal Phase 3 studies.

Improvement in physical function was evaluated using HAQ-DI score, SF-36v2 physical functioning domain score statistically and nominally significant improvements were seen across both these endpoints across all three studies at week 16 and were maintained across week 24 and 52. Improvement in physical function evaluated using HAQ-DI was supported by a change from baseline in the average HAQ-DI score of -0.2 across all three studies for APR30mg BID The HAQ-DI score was also maintained between Week 24 and Week 52.

The results of the ACR20 analysis were supported by the results of the modified PsARC, DAS28[CRP], EULAR good/moderate response) analyses. A positive treatment effect was also observed irrespective of the number or type of prior small-molecule DMARD or biologic used.

A consistent, improvement in modified ACR 20 responses, compared to placebo, was observed irrespective of whether apremilast was given alone (approximately 35% of subjects) or in combination with concomitant small-molecule DMARDs (approximately 65% of subjects).

Improvements in extra articular manifestations of psoriatic disease (PASI-75, MASES, dactylitis severity score), and health-related quality of life (SF-36v2 PCS score, FACIT-Fatigue score) at Weeks 16 and 24, and these improvements were broadly maintained at Week 52 with continued apremilast treatment.

There was no formal comparison of efficacy between the APR 20 BID and APR 30 BID treatment groups but in general higher and more consistent responses were observed for subjects receiving APR 30 BID over APR 20 BID up to week 24 (the placebo –controlled period).

Plaque Psoriasis

Efficacy has been demonstrated for patients with plaque psoriasis for induction at 16 weeks and short maintenance for an additional 16 weeks. Pooled analysis shows a statistical significant difference in favour of Apremilast 30mg bid for PASI 75 at 16 weeks (26.2 % improvement) and s PGA (17.2 % improvement) versus placebo, and 15.9% of patients achieving both PASI 75 and sPGA 0-1 at 16 weeks, with higher efficacy observed at later time points.

Continued treatment shows maintenance of effect of PASI and s PGA in weeks 16 to 32, and patients continued on treatment having significantly longer time before loss of PASI 75, PASI 50 or s PGA is observed at week 32 to 52.

Also patients who were treated with placebo in the randomised withdrawal phase showed significant responses following retreatment with Apremilast 30mg BID.

Uncertainty in the knowledge about the beneficial effects.

Psoriatic arthritis

The pivotal studies are placebo controlled. While this complies with the CHMP guidance and scientific advice it would have been helpful if an active controlled arm had been included. The CHMP however considered that the lack of comparator data does not preclude impact othe B/R of apremilast. The data after stopping therapy (i.e. a randomised withdrawal phase) have not been evaluated in this program this would have been useful in terms of evaluating the effect of withdrawal of treatment on persistence of effect, the possibility of treatment holidays etc. No radiographic evidence of a disease modifying effect with apremilast is available in patients with psoriatic arthritis. The available nonclinical and clinical data (in patients with RA) do not indicate that any unexpected, deleterious effects or MRI evidence of inhibition of structural damage on cartilage, bone, or joints occur following treatment with apremilast.

The treatment effects relative to placebo are modest for the primary and key secondary endpoints. In terms of improvement of non-articular manifestations of psoriatic disease there was very little evidence of a treatment effect in enthesitis as evidenced by the change in MASES scores from baseline.

Inclusion of patients who have a contraindication to a DMARD therapy in the apremilast indication has not been adequately justified. The applicant agreed to update the indication as follows: “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”.

The CHMP also concluded that while apremilast has been shown to improve physical function. The MCID for HAQ-DI in psoriatic arthritis has not been clearly established. The statement: “Otezla has been shown to improve physical function” has therefore been removed from the indication by the applicant.

Plaque Psoriasis

As a higher dose than 30 mg BID was not studied in the phase 2 dose finding study a full characterisation of the dose response has not been shown, however as a clinically relevant effect was demonstrated this does not impact on the B/R of apremilast.

A justification that the efficacy data support a broad indication in patients in need of systemic therapy was considered inadequate, in particular since an active comparator study with a conventional systemic therapy has not been presented for assessment. It is therefore difficult at the present time to put the efficacy of this product into context with other systemic therapies. The applicant has agreed to amend the indication to a second line systemic treatment as follows:"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)".

With prolonged use a lowering and loss of PASI 75 score is observed at 52 weeks compared with maximal scores achieved at 24-28 weeks, this is also observed for s PGA. As psoriasis is a chronic condition which may require prolonged treatment efficacy data beyond 12 months is not known. However longer term safety and efficacy is being explored, both PSOR-008 and PSOR-009 studies are ongoing through their completion up to a total of 5 years of apremilast administration, the applicant will provide the clinical efficacy data after the completion of these studies (as described in the RMP).

Risks

Unfavourable effects

The adverse events and risks related to apremilast have been characterised in a large safety database. The adverse event profile appears similar to other phosphodiesterase 4 inhibitors.

The most frequently reported treatment related adverse events were diarrhoea, nausea, headache, respiratory tract infection and nasopharyngitis. A dose effect was observed for diarrhoea, nausea and headache. The majority of adverse events were of mild to moderate intensity.

Uncertainty in the knowledge about the unfavourable effects

Weight loss of up to 2 kg was also observed in the apremilast treated group. This weight loss could be exacerbated or become clinically significant in subjects with a low BMI who commence treatment or in subjects with persistent diarrhoea or intolerability. This has been addressed in the product information and in the RMP.

The data available regarding exposure in pregnancy is very limited- 11 babies born thusfar. Studies in animals have demonstrated an effect on fetal growth and development. The applicant has updated the product information stating that apremilast is contraindicated in pregnancy. Further information on the potential risks of aprelimast during pregnancy will be provided through the monitoring of planned or unplanned pregnancies exposed to aprelimast in a pregnancy exposure registry in the US. The final study report from this registry will be provided by the applicant (as described in the RMP). 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.

Benefit-risk balance

Discussion on the benefit-risk balance

Psoriatic Arthritis

Apremilast is an orally administered treatment that has demonstrated some benefit in patients with moderate to severe psoriatic arthritis who have been pretreated with DMARDs both small –molecule and biological type. There is evidence that it is efficacious in combination with small molecule DMARD therapy and as a monotherapy. There is some evidence of improvement in function and non-articular

manifestations of psoriatic disease. The clinical significance of magnitude of the improvements in function and in some of the non-articular endpoints is unclear. No comparator data is available. The efficacydemonstrated in the treatment of psoriatic arthritis is modest but a favourable safety and tolerability profile, and along with the benefit of an oral route of administration could result in better patient compliance with treatment. The CHMP is of the opinion that a second line use of apremilast in the treatment of psoriatic arthritis in patients who have failed treatment or can't tolerate first line treatment is approvable.

Plaque Psoriasis

Apremilast provides a novel oral therapeutic agent for the treatment of moderate to severe plaque psoriasis patients who are in need of systemic therapy. The pivotal studies achieved the primary and key secondary objective as a statistically significant improvement in plaque psoriasis was seen following treatment with Apremilast 30 mg BID. The efficacy demonstrated in the treatment plaque psoriasis is modest but considering the favourable safety and tolerability profile and along with the benefit of an oral route of administration, could result in better patient compliance with treatment. A justification that the efficacy and safety data support a broad indication in patients in need of systemic therapy was considered inadequate, in particular since an active comparator study with a conventional systemic therapy has not been presented for assessment. It is therefore difficult at the present time to put the efficacy and safety of this product into context with other systemic therapies. The applicant has agreed to amend the indication to a second line systemic treatment as follows:"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)".

Adverse events for patients exposed up to 12 months have been identified however the majority of adverse event were mild to moderate intensity. Longer term safety data is being collected and forms part of the RMP .The applicant has updated the product information stating that apremilast is contraindicated in pregnancy. Further information on the potential risks of aprelimast during pregnancy will be provided through the monitoring of planned or unplanned pregnancies exposed to aprelimast in a pregnancy exposure registry (as described in the RMP).

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Otezla in the treatment, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy and 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) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

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.

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

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that apremilast is qualified as a new active substance.