Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Apremilast

Proprietary Product Name: Otezla

Sponsor: Celgene Pty Ltd

First Round CER report: 18 July 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings extracted from the Clinical Evaluation Report (CER). This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
AE	Adverse Event
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredient
APR	Apremilast
BMI	Body Mass Index
BSA	Body Surface Area
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	Confidence interval
CL/F	Apparent Clearance
CMH	Cochran-Mantel-Haenszel
CrCL	Creatinine Clearance
CRP	C-Reactive Protein
CsA	Cyclosporine
CS	Corticosteroids
CV	Coefficient of Variation
DLQI	Dermatology Life Quality Index
DMARD	Disease Modifying Anti-Rheumatic Drug
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
IL	Interleukin
LEF	Leflunomide
LOCF	Last Observation Carried Forward
LS	Least Square

Abbreviation	Meaning
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	Minimal Clinically Important Difference
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Index
NSAID	Non-steroidal Anti-inflammatory Drug
NRI	Non-Responder Imputation
PASI	Psoriasis Area Severity Index
PBO	Placebo
PD	Pharmacodynamic
PDE	Phosphodiesterase
PhGA	Physician Global Assessment
PK	Pharmacokinetic
PsA	Psoriatic Arthritis
PSOR	Psoriasis
PT	Preferred Term
PtGA	Patient Global Assessment
PY	Patient-Years
QOL	Quality of Life
SAE	Serious Adverse Event
sPGA	static Physician Global Assessment
scPGA	scalp Physician Global Assessment
SD	Standard Deviation
SOC	System Organ Class
SSZ	Sulfasalazine
TNF	Tumour Necrosis Factor

Abbreviation	Meaning
ULN	Upper Limit of Normal
V/F	Apparent Volume of Distribution

1. Background

1.1. Submission type

This is a full submission to register a new chemical entity, apremilast (APR), for the treatment indications of psoriatic arthritis (PsA) and psoriasis (PSOR) in adult patients. The sponsor application letter is dated 5 March 2014.

The submission contains 5 clinical efficacy/safety studies for the requested indication of PsA. This includes a supporting Phase II trial (Study PSA-001), 3 replicate pivotal Phase III controlled trials in subjects with active PsA despite conventional and/or biologic DMARDs (Studies PSA-002, PSA-003 and PSA-004), and another pivotal Phase III trial in adult patients with active PsA who were DMARD naïve (Study PSA-005). Studies PSA-002, PSA-003 and PSA-004 evaluated APR as a monotherapy or in combination with conventional DMARDs and were designed with similar schema, eligibility criteria, as well as doses and regimens of therapy. Study PSA-005 evaluated APR as monotherapy. The submission included data collected up to 52 weeks for Studies PSA-002, PSA-003 and PSA-004, and up to 24 weeks in Study PSA-005 (although the planned duration of treatment follow-up is 52 weeks in this trial). The studies were designed to evaluate the effect of APR on PsA signs and symptoms, physical functioning and health related quality of life (QOL).

For the indication of PSOR, the submission contained 6 clinical studies: 2 open-label Phase II trials (Studies PSOR-001 and PSOR-004), 2 randomized Phase II trials (Studies PSOR-003 and PSOR-005) and 2 pivotal Phase III trials (Studies PSOR-008 and PSOR-009). In this submission, the 2 pivotal Phase III studies collected data up to 52 weeks and the primary efficacy endpoint for evaluating improvement in PSOR was the proportion of subjects achieving PASI 50 or PASI 70 response at week 16.[1] In addition, subjects were secondarily evaluated for dermatology related QOL outcomes.

In support of the submission, the pharmacology of APR has been characterised in 16 clinical pharmacology studies, with pharmacokinetic (PK) features additionally examined in the Phase III clinical trial program in both PsA and PSOR.

1.2. Drug class and therapeutic indication

APR is an oral small molecule inhibitor of phosphodiesterase 4 (PDE4), which acts intracellularly to modulate various pro-inflammatory and anti-inflammatory mediators. It has the ATC code L04AA32, which relates to selective immunosuppressant drugs.

The proposed indications are:

> *"For the treatment of active psoriatic arthritis in adult patients."*
>
> *"For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy."*

[1] The primary endpoint for both pivotal studies was the proportion of patients achieving a PASI 75 response.

1.3. Dosage forms and strengths

The submission proposes registration of the following dosage forms and strengths: 10mg (pink), 20mg (brown) and 30 mg (beige) tablets. The tablets are presented in 3 pack types. There is an initial 2-week titration pack containing 4 x 10mg tablets, 4 x 20mg tablets and 5 x 30 mg tablets for the first week of treatment followed by 14 x 30 mg tablets for the second week of therapy. The other proposed pack sizes of 30mg tablets are 56 (4 weeks) and 168 (12 weeks).

1.4. Dosage and administration

For both proposed treatment indications, the recommended dose of APR is 30mg twice daily, taken orally approximately 12 hours apart. An initial titration scheduled as outlined in Table 1 is recommended. No re-titration is required after initial titration. APR tablets should be swallowed whole, either with or without food. No dose adjustment is required in older patients, those with hepatic impairment or patients with mild or moderate renal impairment. The maintenance dose of APR should be reduced to 30mg once daily in patients with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min). For initial dose titration in this patient group, it is recommended that APR be taken using the AM (morning) schedule only, and the PM doses should be omitted.

Table 1: Recommended Initial Dose Titration Schedule for Apremilast

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

2. Clinical rationale

PsA is a chronic inflammatory arthritis associated with skin psoriasis which typically onsets between the ages of 30 and 55 years, and affects men and women equally. Skin PSOR has prevalence in the general population of 2 - 3%, and it is estimated that approximately 30% of patients with skin PSOR develop PsA (Mease, 2011). PsA is a multifaceted and heterogeneous disease, which affects the joints, soft tissues (enthesitis and dactylitis) and skin. All of the disease manifestations may impact upon functional capacity and QOL. There is also increased mortality with persistent, severely active PsA. Peripheral joint involvement with PsA may be polyarticular (35 - 40%) or oligoarticular (20 - 35%), and axial involvement (spondylitis) has been reported in 10 - 25% of patients. Current approved treatment options in Australia for moderately to severely active PsA include NSAIDs; conventional non-biological DMARDs such as methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF) and cyclosporine (CsA); as well as several anti-TNF drugs. Recent literature suggests that conventional DMARDs have modest efficacy in treating the signs and symptoms of PsA. In addition, while anti-TNF drugs have been shown to demonstrate significant efficacy in treating active PsA, a substantial proportion of patients are not achieving meaningful American College of Rheumatology (ACR) responses. Based on the current literature for anti-TNF therapies, ACR20 response rates range from 50 - 60% and ACR50 response rates are approximately 30 - 40%. As such, there is an unmet need for additional therapies for active, treatment refractory PsA.

PSOR is a common, inflammatory and proliferative skin disease with a genetic determinant. Although PSOR may occur at any age, 2 age peaks of onset are identified: second decade of life (early onset) and fifth decade (late onset). Chronic stable plaque PSOR (PSOR vulgaris) is the most common form of the disease, accounting for 85 - 90% of all cases. While the majority of patients have mild PSOR, studies have found that 25% of patients reported their disease as moderate, and 10% as severe. PSOR can be disabling, affecting the physical, social and

psychological well-being of patients. Plaque PSOR manifests as thickened, well-demarcated, erythematous patches of skin covered with silvery scales. The lesions often arise in predisposed areas such as the extensor aspects of the knees and elbows, but can be generalised. Other sites affected by PSOR include the nails, scalp, palms, soles and intertriginous areas. The skin lesions frequently cause symptoms of pruritus and discomfort. Topical agents such as salicylic acid, corticosteroids (CS) and vitamin D analogues are often used as a first line therapy, particularly if the PSOR is localised. Phototherapy with UVB or psoralen + UVA is often used as a first line treatment for widespread PSOR, or as a second line treatment if topical therapy is insufficient. Systemic treatment with oral retinoids, MTX and CsA are indicated in severe forms of PSOR. All of the systemic treatments have demonstrated efficacy but their long-term use is limited by potential risks and toxicities. Biologic therapies such as anti-TNF drugs and ustekinumab have been demonstrated to be highly effective in the treatment of moderate to severe PSOR but their use is limited by the risk of significant Adverse Events (AEs) such as serious infection and malignancy potential. Despite the variety of treatment options available in PSOR, patients are often dissatisfied (> 70% prevalence) with current therapy options due to lack of sustained efficacy, adverse events and/or treatment inconvenience. Hence, there is an unmet need for additional therapies for moderate to severe PSOR, which is refractory to topical treatment.

APR is a novel, oral, small molecule inhibitor of PDE4 that works intracellularly to modulate a network of pro- and anti-inflammatory mediators, and has a different mechanism of action to conventional DMARDs, systemic therapies and biologic drugs. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. Inhibition of PDE4 elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of Tumour Necrosis Factor (TNF), Interleukin (IL)-23, IL-17, and other pro-inflammatory cytokines. Elevation of cAMP also increases anti-inflammatory cytokines. These pro- and anti-inflammatory mediators have been implicated in PSOR and PsA. IL-23 induces the T-helper 17 (Th17) pathway and promotes the secretion of various other pro-inflammatory cytokines such as IL-17, IL-21 and IL-22. IL-23 is highly expressed in the synovium and entheses of patients with PsA, and patients with PSOR over-express these cytokines in plaques. Overall, APR appears to have robust biological plausibility in being able to treat both PSOR and PsA through inhibition of the TNF, IL-23 and Th17 cytokine pathways, which are central to the pathology of the diseases (Schett et al, 2013).

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 16 clinical pharmacology studies, including 15 that provided pharmacokinetic data and 1 that provided pharmacodynamic data.
- 5 population pharmacokinetic analyses – using datasets collected in Studies PSA-001, PSA-002, PSOR-005, PSOR-008 and RA-002.
- 6 pivotal efficacy/safety studies – 4 relating to the PsA indication (Studies PSA-002, PSA-003, PSA-004 and PSA-005) and 2 for the PSOR indication (PSOR-008 and PSOR-009).
- 2 dose-finding studies – 1 in PsA (Study PSA-001) and 1 in PSOR (Study PSOR-005).
- 3 other efficacy/safety studies conducted in adult subjects with PSOR (Studies PSOR-001, PSOR-004 and PSOR-003). In addition, the submission contained 3 clinical studies in different patient groups as supporting safety and PK data. These studies were ASTH-001 (mild asthma), BCT-001 (Behcet's Disease) and RA-002 (Rheumatoid Arthritis).

- No pooled analyses or meta-analyses were part of this submission; however, the sponsor provided a comparison and analysis of the results across the similarly designed and conducted Phase III trials in each of the proposed treatment indications.[2]

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

All of the studies in the APR clinical development program for the treatment and prevention of PsA and PSOR were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

A total of 16 clinical pharmacology studies in humans have been conducted with APR, 13 of which were in healthy subjects (n = 422) and 3 trials were in non-healthy subjects (n = 39). The non-healthy subjects comprise 15 subjects with PsA or rheumatoid arthritis (RA), 8 subjects with severe renal impairment and 16 subjects with hepatic impairment. In the non-crossover studies, 108 subjects received a single dose of APR and 75 subjects received multiple doses of APR. In the crossover trials, 143 subjects received single doses and 110 subjects received multiple doses of APR.

All of the clinical pharmacology studies have been completed. Table 2 shows the studies relating to each pharmacokinetic (PK) topic and the location of each study summary. None of the PK studies had deficiencies that excluded their results from consideration.

[2] No pooled analyses were conducted for efficacy. But for safety, data across the studies were pooled.

Table 2: Submitted Pharmacokinetic Studies for Apremilast

PK topic	Subtopic		Study ID
PK in healthy adults	General PK	- Single does	PK-001
			PK-002
		- Multi-dose	PK-001
			PK-007
	Bioequivalence†	- Single dose	CP - 012
		- Multi-dose	BA-001 and BA-002
	Food effect		BA-001 AND BA-002
			CP-022
PK in special populations	Target population §	- PSOR	PSOR-001,004,005, 008 and 009
	(multi-dose)	- PsA	PSA-001 and PSA-002
	Hepatic impairment		CP-011
	Renal impairment		CP-019
	Age related differences		CP-024
Genetic and Gender-related	Gender		CP-024
	Race/ Ethnicity		CP-018
PK interactions	Rifampicin		CP-025
	Ketoconazole		PK-005
	Oral Contraceptive		CP-020
	Methotrexate		PK-010
Population PK analyses	Healthy subjects		BA-001, BA-002, PK-008, CP-022, and CP-024
	Target population	- PsA	PSA-001 and PSA-002
		- PSOR	PSOR-005 and PSOR-008
	Other – RA		PK-010 and RA-002

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive APR if approved for the proposed treatment indications.

Of the 16 clinical pharmacology studies:

- Nine were single-dose studies in healthy subjects that evaluated the PK, bioavailability, food effect, drug interaction with ketoconazole and rifampicin, and the effects of age, gender, and ethnicity (Japanese/Chinese/Caucasian) on PK.
- Two were single-dose trials in non-healthy subjects that evaluated the effect of hepatic or renal impairment on the PK of APR.
- Four were multiple-dose studies in healthy subjects that evaluated PK, drug interaction with oral contraceptives (OC), and 1 trial was a thorough assessment of the effect of APR on the QT interval corrected (QTc). The QTc interval study (PK-008) will be covered in the pharmacodynamic section of this report.
- One was a multiple-dose study in non-healthy (special population) subjects that evaluated the PK interaction with MTX in subjects with PsA or RA.

In addition, the PK of APR was also evaluated in 9 of the Phase II or III studies in subjects with PsA, PSOR, asthma and RA.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies in humans.

4.2.1. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summaries in Module 2. APR is the S-enantiomer of N-[2-[(1S)-1-(3-ethoxy-4 - 4methoxyphenyl)-2-(methylsulfonyl) ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl] acetamide. It has a molecular weight of 460.5 g/mol. APR is an insoluble compound at 370C. It has a partition coefficient of 58.4, and demonstrates a marginal preference for lipophilic solvents.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

4.2.2.1.1. Sites and mechanisms of absorption

Data from the mass balance study (PK-002), and the absolute bioavailability study (CP-012) indicate that APR is rapidly and well absorbed into the systemic circulation following oral administration, with a Tmax of 1 - 3 hours and an absolute bioavailability of 73.2%.

Study PK-002 was a Phase I, open-label, single centre study in 6 healthy male subjects in USA, aged 19 to 55 years inclusive, which aimed to characterise the metabolic profile of APR. Subjects were confined to study centre for 10 days, and given a single 20mg oral suspension of APR containing [14C] after an overnight fast. Serial samples of blood and excreta were collected to assess the distribution and elimination of radioactivity. Based on the mass balance of specimens, APR was well absorbed following oral suspension dosing with 57.9% and 39.2% of the orally administered dose being recovered from the urine and faeces, respectively. The absolute bioavailability of APR was calculated to be 73.2%, which was derived from the sum of urine and faecal radioactivity of intact APR (versus APR metabolites recovered from both sources).

Study CP-012 was a single centre, open-label, 5-period, partly randomized (fixed treatment for the first period followed by randomized treatment sequences for the other 4 periods), 5-way crossover study conducted in 12 healthy male subjects (9 completed) in Britain between 18 and 50 years to evaluate the absolute bioavailability and regional absorption of oral APR. An intravenous microtracer dose of APR (100µg) labelled with [14C] was administered 1.75 hours after the ingestion of a single oral APR 20mg dose (immediate release formulation). The results indicated that oral absorption of APR occurs at all regions of the gastrointestinal tract, with the relative bioavailability being 93% in the proximal small intestine, 77% in the distal small bowel and 51% in the colon. The progressive regional decrease along the gastrointestinal tract in the relative bioavailability of APR was due to a solubility/dissolution effect.

4.2.2.2. Bioavailability

4.2.2.2.1. Absolute bioavailability

Study CP-012 demonstrated that APR has an absolute bioavailability of 73.2%.

4.2.2.2.2. Bioequivalence of clinical trial and market formulations

A total of 4 different APR formulations have been used in clinical studies, and the sponsor intends to commercialise 10mg, 20mg and 30mg film coated tablets using Formula 4. The clinical programs started with a capsule formulation (Formula 1). This was used in 3 Phase II PSOR trials (Studies PSOR-001, PSOR-003 and PSOR-004) as well as 1 Phase II PsA study (PSA-001). Micronized active substance was initially used in the capsule formulation. Particle size distribution of micronized active pharmaceutical ingredient (API) ranged from 2µm to 4µm in diameter. Capsules containing micronized API were also used in the Phase I PK studies (PK-001, PK-005 and PK-007). A relative bioavailability study (BA-001) was conducted to compare capsules with micronized API (reference product) versus milled API (test formulation). Study

BA-001 was an open-label trial conducted at a single centre in the UK which recruited 12 healthy males between the ages of 23 and 38 years (mean age of 28 years). All subjects completed the trial. This study demonstrated that for a capsule made with milled API versus micronized API had approximately 83% and 92% bioavailability under fasting and fed conditions, respectively. Bioavailability was assessed by plasma PK of APR Cmax, Tmax and AUC in 12 young healthy male subjects given single 20mg doses of APR in this single centre, randomized open-label study. As a result, the micronization step was removed from the manufacturing process. The non-micronized API batches manufactured to date range in particle size from 6µm to 29µm.

A white round tablet formulation (Formula 2) was then developed for use in the clinical trials. Formula 2 was used in Study PSOR-005 (initial trial phase as well as both extension periods). This formulation contained the same ingredients as the capsules, with the exception that the tablets contain microcrystalline cellulose while the capsules contain silicified microcrystalline cellulose. A comparative bioavailability study (BA-002) was conducted to evaluate the relative bioavailability of APR tablets versus capsules. This study demonstrated that the tablet versus capsule presentations had 112% and 105% bioavailability under fasting and fed conditions, respectively (Table 3).

Table 3: Comparison of Apremilast Pharmacokinetic Parameters in Studies BA-001 and BA-002

Study #	Formulation / Dose	Condition	Pharmacokinetic Parameters			
			C_{max} (ng/mL)	AUC_{∞} (ng·h/mL)	*t_{max} (hour)	$t_{1/2}$ (hour)
CC-10004-BA-001	Capsule (milled) / 20 mg	Fasting	154.3	1372.4	2.0	8.0
CC-10004-BA-002	Capsule/ 40 mg	Fasting	190.9 [a]	1876.0 [a]	3.0	7.3
CC-10004-BA-001	Capsule (milled) / 20 mg	Fed	135.1	1696.1	6.0	6.9
CC-10004-BA-002	Capsule/ 40 mg	Fed	166.8 [a]	2066.0 [a]	4.0	5.9
CC-10004-BA-002	Tablet/ 40 mg	Fasting	212.7 [a]	2070.3 [a]	3.0	6.6
CC-10004-BA-002	Tablet/ 40 mg	Fed	209.5 [a]	2157.5 [a]	4.0	5.3

*Median, [a] Normalized to 20-mg dose

Study BA-002 was a single centre (Canada), open-label, randomized, 4-period crossover study that evaluated the relative bioavailability of APR administered as orally as a 40mg tablet versus 2 x 20mg capsules (with and without food) in 16 healthy male subjects aged between 20 and 49 years (mean age of 35 years). Subjects were randomised to 1 of 4 sequences (i.e. 4 subjects to each sequence of 4 treatment periods). There was a washout period of 5 - 7 days between each treatment period. Relative bioavailability was assessed using the plasma PK characteristics of Cmax, Tmax and AUC in each of the allocated treatments. The 40mg APR tablets were the test product and the 2 x 20mg capsules were the reference formulation. A total of 14 subjects completed the study.

Formula 3 was used in all of the Phase III PsA and PSOR trials as well as Study RA-002. It consists of modified diamond shaped tablets with colour coats differentiating each tablet strength. The compositions of the core tablets are the same as for Formula 2. The difference relates to the addition of a colorant in the film coat and the quantity of film coat that is applied.

The film coating is non-functional. Tests have been performed to confirm that the comparative dissolution of Formula 2 and 3 are identical. Hence, the sponsor has not conducted an in vivo bioequivalence study.

Tablets produced using Formula 4 have the same core tablet composition as Formula 3, and are manufactured by the same process. The difference between Formulas 3 and 4 relates to the film coating. The modified coating in Formula 4 eliminates the colour fading observed during stability studies of Formula 3. The sponsor has conducted in vitro dissolution studies comparing Formulas 3 and 4 (10mg and 30mg tablets) and found no significant differences in dissolution. The 30mg tablets of Formula 4 were used in a food effect study (CP-022).

4.2.2.2.3. Influence of food

Study CP-022 demonstrated that food intake had no effect on the bioavailability of a single 30mg dose of orally administered APR (commercial formulation). This was a single centre, open-label, randomised, 2-period, 2-sequence crossover trial, which enrolled a total of 46 subjects (44 [95.7%] completed the study). Each subject was randomised to receive a single dose of APR under fasting and fed conditions across 2 study periods. There was a 5-10 day washout period between study periods. For both study periods, subjects fasted for at least 10 hours prior to drug ingestion. In the fasted treatment period, subjects were only allowed water up to 1 hour prior to dosing, and at least 1 hour after dosing. They remained fasted for 4 hours post-dose. During the fed treatment period, subjects consumed a standard high fat breakfast (as per FDA guidelines) within 30 minutes of dosing and resumed fasting (except water) for 4 hours post-dosing. Serial blood samples were collected prior to each dose administration and for up to 48 hours post-dose. PK parameters were calculated from plasma concentration-time data using non-compartmental methods.

The median Tmax of APR in the fasted state was 2.5 hours (range: 0.62 - 5.02 hours; n = 45) and 3.0 hours when fed (range: 1.0 - 8.0 hours; n = 44). Apparent clearance and T1/2 (7.99 hours in the fed group and 8.88 hours in the fasted arm) were similar between the 2 groups. The AUC and Cmax of APR were comparable under fasted and fed conditions with the 90% CIs of the geometric mean ratios for each PK variable fully contained within the range of 80-125%, indicating no effect of food on APR bioavailability and plasma exposure.

4.2.2.2.4. Dose proportionality

Across the clinical pharmacology studies, APR demonstrated consistent and comparable dose-proportional exposure in healthy subjects. Studies PK-001 and PK-007 were the 2 Phase I trials that principally delineated the dose proportionality of APR in healthy subjects. Both studies were double-blind, PBO-controlled trials investigating ascending multiple oral doses of APR.

Study PK-001 was conducted at a single centre, and recruited 40 young healthy male subjects aged between 19 and 47 years (inclusive). The subjects were studied in 5 groups of 8. Five dose levels of APR were given as capsules: 10mg, 20mg and 40mg – all given once daily; 80mg/day (given as 40mg twice daily); and 100mg/day (given as 50mg twice daily). At each of the planned dose levels, 6 subjects received APR and 2 received PBO in the fasted state. Each subject received a single oral dose followed by multiple oral doses over a 5-day period. Blood samples for PK analysis were collected pre-dose and for 48 hours post-dose on days 1 and 7 or 12.

Table 4 summarises the results of Study PK-001. The median Tmax for APR occurred at 1-3 hours. Following Cmax, plasma concentrations of APR declined in an apparent biphasic manner. The mean apparent elimination T1/2 was 5 - 7 hours, and similar for each dose and day of study. There was no accumulation of APR following 10mg-40mg once daily dosing and only slight accumulation following 40mg-50mg twice daily administration. Systemic exposure to APR (as determined by AUC∞ and AUCt) increased in a dose proportional manner. However, Cmax on day 1 across all doses increased in a less than dose proportional relationship.

Table 4: Apremilast Pharmacokinetic Parameters in Study PK-001

Parameter (Unit)	Total Daily Dose of Apremilast									
	10 mg		20 mg		40 mg		80 mg[a]		100 mg[b]	
	Day 1 (N = 6)	Day 12 (N = 6)	Day 1 (N = 6)	Day 7 (N = 6)	Day 1 (N = 6)	Day 7 (N = 6)	Day 1 (N = 6)	Day 7 (N = 6)	Day 1 (N = 6)	Day 7 (N = 6)
AUC_τ (ng·h/mL)	1085 (16.6)	998 (22.8)	1854 (39.2)	1948 (42.0)	3225 (47.8)	3289 (45.1)	3270 (45.6)	4482 (34.7)[c]	4315 (29.3)	5164 (38.6)
AUC_∞ (ng·h/mL)	1153 (18.0)	NC	1908 (40.8)	NC	3379 (47.1)	NC	4106 (42.0)	NC	5407 (32.4)	NC
C_{max} (ng/mL)	206 (32.3)	180 (29.9)	347 (36.6)	419 (40.1)	533 (35.9)	490 (52.4)	592 (49.0)	881 (30.8)	688 (43.4)	994 (29.5)
t_{max} (h)[c]	1.00 (0.500 - 2.00)	2.00 (1.50 - 2.50)	1.75 (1.00 - 4.02)	1.00 (1.00 - 2.50)	2.05 (1.50 - 3.00)	2.75 (2.00 - 3.00)	2.25 (1.00 - 3.00)	2.50 (1.00 - 3.00)	3.00 (1.50 - 6.02)	2.00 (1.50 - 2.03)
C_{trough} (ng/mL)	5.95 (64.1)	4.30 (92.6)	5.22 (222)	4.94 (117)	18.5 (54.2)	15.9 (104)	102 (44.4)	116 (91.0)[c]	152 (33.2)	107 (66.7)
$t_{1/2}$ (h)[d]	6.54 (19.9)	5.26 (33.7)	4.45 (33.2)	4.46 (28.7)	6.04 (31.0)	5.82 (47.2)	5.56 (23.5)	6.16 (22.1)[c]	5.56 (20.7)	6.84 (18.7)
CL/F (mL/min)	145 (18.0)	167 (22.8)	175 (40.8)	171 (42.0)	197 (47.1)	203 (45.1)	162 (42.0)	149 (34.7)[c]	154 (32.4)	161 (38.6)
Vz/F (L)	81.8 (25.2)	76.1 (51.1)	67.3 (33.6)	66.1 (51.0)	103 (73.4)	102 (48.2)	78.2 (57.4)	79.3 (46.3)[c]	74.2 (28.5)	95.5 (43.7)
$fe_{(0-\tau)}$ (%)	1.29 (42.6)	1.87 (25.9)	NA	NA	NA	NA	NA	NA	NA	NA
$CL_{R(0-\tau)}$ (mL/min)	1.98 (41.9)	NA	NA	NA	NA	NA	NA	NA	NA	NA

AUC_∞ = area under the plasma concentration versus time curve from time zero to infinity; AUC_τ = area under the plasma concentration versus time curve over the dosing interval; CL/F = apparent total plasma clearance; $CL_{R(0-\tau)}$ = renal clearance over the dosing interval; C_{max} = maximum plasma concentration; C_{trough} = plasma concentration at the end of the dosing interval; $fe_{(0-\tau)}$ = percentage of the dose excreted in urine over the collection interval; N= total number of subjects; NA = not applicable; NC = not calculated; τ = 12 hours; $t_{1/2}$ = apparent plasma terminal elimination half-life; t_{max} = time to maximum concentration; Vz/F = apparent volume of distribution during the terminal phase.

[a] Single dose of 40 mg on Days 1 and 7, BID dosing on Days 3 to 6.

[b] Single dose of 50 mg on Days 1 and 7, BID dosing on Days 3 to 6.

[c] Median (minimum – maximum)

[d] N = 5

Note: Geometric Mean (Geometric %CV) except where otherwise noted.

Study PK-007 was conducted at a single centre, and enrolled 55 young healthy male subjects (53 completed the study and 44 were included in the PK analysis). The subjects were studied in 5 groups of 11 subjects. Five dose levels of APR were given as capsules: 40mg, 60mg, 80mg and 100mg –all given once daily; and 80mg/day given as 40mg twice daily. However, due to AEs that were considered dose limiting at the time of this study (2006), subjects were not dosed at 100mg/day. The study also explored the possibility of dose titration to reduce the frequency and severity of gastrointestinal AEs, so the group that were randomized to receive APR 40mg once daily had an initial dose titration schedule (10mg once daily on days 1 - 3, 20mg once daily on days 4 - 6 and 40mg once daily on days 7 - 14). In each dose group, 9 subjects received APR and 2 received PBO in the fasted state for 14 days. Blood samples for PK analysis were collected pre-dose and 2 hours post-dose on days 1 - 9, pre-dose on days 10 - 12, and intensively for up to 48 hours post-dose on day 14.

At the tested doses, the median Tmax for APR was 2-4 hours post-dose on days 1 and 14. Across all dose levels and days (1 and 14), the mean T1/2 for APR was similar at between 6 and 9 hours. Across the dose range of 40mg to 80mg once daily, the total systemic exposure to APR (mean AUC∞ or AUCt) appeared to increase in a dose proportional manner.

4.2.2.2.5. Bioavailability during multiple-dosing

In Studies PK-001 and PK-007, APR was rapidly absorbed at a consistent rate on days 1 and 14 in the groups which received multiple doses of APR (across the daily dose range of 10mg - 80mg).

4.2.2.3. Distribution

4.2.2.3.1. Volume of distribution

Study CP-012 administered a 15-minute IV infusion of 100µg of APR labelled with [14C] and compared it with a single 20mg dose of oral suspension to derive various PK parameters (Table 5). The observed geometric mean (with geometric CV%) for volume of distribution based on area, i.e. Vz, was 87L (22.5%) and exceeds the value for total body water in a 70kg man (approximately 42 L), which suggests that APR is readily distributed from plasma into the tissue space.

Table 5: Summary of Pharmacokinetic Parameters (Geometric Means, Geometric CV %) for Apremilast following IV and Oral Administration in Study CP-012

Treatment	t_{max}[a] (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{∞} (ng·h/mL)	CL (mL/min)	Vz (L)	F_{abs} (%)
Oral apremilast	2.29 (1.00 -4.00)	173 (27.2)	7.63 (1.14)	1480 (21.8)	230 (46.4)	NA	73.2 (12.5)
IV [^{14}C]-apremilast	0.25 (0.25 -0.33)	4.91 (27.2)	6.19 (1.21)	10.1 (22.8)	169 (41.6)	87.0 (22.5)	NA

AUC_{∞} = area under the concentration-time curve from oral or IV dosing to infinity; CL = total clearance; C_{max} = maximum plasma concentration; F_{abs} = absolute bioavailability based on AUC_{∞}; $t_{1/2}$ = terminal half-life; t_{max} = time to reach maximum plasma concentration; V_z = volume of distribution based on area

[a] t_{max} is summarized by median and range (minimum – maximum)

4.2.2.3.2. Plasma protein binding

Pre-clinical studies have shown that APR is moderately bound in human plasma (approximately 68%), and the binding is concentration independent in the concentration range of 0.25 - 2.5 µg/mL.

4.2.2.4. Metabolism

4.2.2.4.1. Interconversion between enantiomers

A pre-clinical study demonstrated that there is no conversion from APR to its stereoisomer (R-enantiomer).

4.2.2.4.2. Sites of metabolism and mechanisms/enzyme systems involved

APR is primarily eliminated as metabolites formed by both cytochrome P450 (CYP)-mediated oxidative metabolism (and subsequent glucuronidation), non-CYP dependent N-deacetylation and non-CYP mediated hydrolysis. CYP3A4, 1A2 and 2A6 all participate in APR metabolism. The effect of APR on CYP3A4 and potential interacting drugs has been focus of the human PK studies.

In pre-clinical studies, APR is a substrate and weak inhibitor of p-glycoprotein (P-gp). However, in vitro data indicates that APR can only inhibit P-gp at a concentration approximately 5 times that achievable by the proposed commercial dose of 30mg twice daily. P-gp does not appear to limit the absorption of APR from the gastrointestinal tract. In addition, as the minority of APR is excreted in its unchanged form, P-gp does not appear to play a significant role in the elimination of APR. APR is not a substrate for other drug transport systems such as breast cancer resistance protein, organic anion transporting polypeptide and multidrug resistance protein.

4.2.2.4.3. Metabolites identified in humans

Consistent with the results from in vitro studies, APR is extensively metabolised in 6 healthy male subjects in Study PK-002, with the majority of [14C]-APR related radioactivity recovered as up to 23 metabolites (90% of total administered dose) in the plasma, urine and faeces. The major metabolic pathway for APR is O-methylation (approximately 50% of the parent drug is metabolised via this pathway). A glucuronide conjugate of O-demethylated APR (M12) is the major circulating metabolite and its urinary excretion was approximately 34% of the total administered dose. Other significantly detected metabolites include M11, M13, M14 and M16. All other metabolites were unquantifiable. All of the metabolites (including M12) are pharmacologically inactive, apart from 2 minor metabolites. The in vivo activity of APR is attributable to the parent compound.

4.2.2.5. Excretion

4.2.2.5.1. Routes and mechanisms of excretion

As demonstrated in Study PK-002, < 3% of the dose of APR is excreted via the kidneys as unchanged APR. The mean total urinary and faecal recovery of [14C]-APR and its metabolites is

97.1%, with the mean contributions being 57.9% in the urine and 39.2% in the faeces. Urinary radioactive excretion of APR is almost complete by 72 hours after a single oral dose, and most faecal excretion occurs by 120 hours.

Following IV administration, APR has a mean total clearance of approximately 10L/hour (Study CP-012) and a terminal elimination half-life (T1/2) of 6 - 9 hours. The majority of total clearance is due to metabolic clearance, and the renal clearance of intact APR is 0 – 1 - 0.3 L/hour (Studies PK-001 and PK-007).

4.2.2.6. Intra- and inter-individual variability of pharmacokinetics

The submission does not contain a summary assessment of the intra-subject and inter-subject variability for the PK of APR, however there are several Phase 1 studies where such data was collected. From a review of each study's individual results APR appears to have moderate intra-subject variability for Cmax (CVs frequently > 40%) and AUC∞ (CVs frequently > 40%). The inter-subject variability appears to be slightly higher. It is also unclear if the different formulations tested and/or tablet strengths demonstrate significant intra- and/or inter-subject variability.

4.2.3. Pharmacokinetics in the target population

The population PK analyses of data collected in healthy subjects compared with patients with PsA identified that subjects with PsA had approximately 36% slower apparent clearance (CL/F) of APR than healthy subjects. Moreover, female subjects (46% of all subjects) with PsA were found to have 16% slower clearance than male subjects with PsA (Study PSA-002). In addition to the disease status (PsA), gender and body weight have also been identified to be statistically significant covariates that affect APR exposure. Subjects with higher body weight tend to have faster clearance and a larger volume of distribution. Simulations based on extremely low and high body weights in males and females suggest that body weight and gender effects combined are small relative to the intrinsic variability of APR, and therefore the sponsor proposes that no dose adjustment is required for these reasons.

Population PK analysis of APR exposure data indicates that APR clearance is 7.4L/hour in subjects with PSOR (Study PSOR-005; 63% male and 37% female) compared to approximately 10L/hour in healthy subjects (Study CP-012). In the population PK analysis of Study PSOR-005, lean body weight (calculated on body weight and gender) was identified to be a significant covariate affecting APR clearance in subjects with PSOR. Study PSOR-008 also demonstrated that gender and disease status were statistically significant covariates impacting upon the CL/F of APR. Overall, CL/F was about 20% slower in subjects with PSOR compared with healthy subjects, and approximately 31% slower in female subjects than in male subjects. This is consistent with the gender and body weight effect on APR clearance identified in the population PK analyses of the combined APR data in healthy subjects, and subjects with RA (Study RA-002) and PsA (Study PSA-002).

In a separate population PK analysis (Study RA-002) of combined APR exposure data from healthy subjects and subjects with RA, subjects with RA had 32% slower clearance than healthy subjects. Female subjects with RA were found to have about 13% slower clearance than male subjects with RA. In addition to the disease status of RA and gender, the population PK analysis identified body weight as a significant covariate that affected APR exposure. Subjects with higher body weight tend to have faster clearance and larger volume of distribution. Simulations based on extremely low and high body weight in males and females suggest that body weight and gender effects combined are small relative to the intrinsic variability of APR.

The PK parameters for APR are similar in patients with PsA (Study PSA-002), PSOR (Studies PSOR-005 and PSOR-008) and RA (Study RA-002). The results for the CL/F of APR in subjects with PsA, RA and PSOR are similar at 7.34 L/hour, 7.6 L/hour and 7.4 L/hour, respectively). This indicates that the presence of inflammatory autoimmune disease involving the skin and/or joints impacts on the PK of APR. Based on the clinical efficacy results of the pivotal phase 3

studies, this small CL/F difference in subjects with disease versus healthy subjects has no appreciable clinical impact. Furthermore, the sponsor asserts that the effect of gender on CL/F lies within the expected between-subject variability for CL/F, and no dose adjustment by gender is required. The potential effect of body weight upon clinical efficacy outcomes was not observed in any of the Phase 3 studies apart from Study PSA-005, whereby subjects weighing > 100kg had no significant treatment related effect with APR over control therapy.

Regarding other intrinsic factors, the PK characteristics of APR demonstrate no differences based on ethnicity, and are not affected by hepatic impairment. Mild to moderate renal impairment also does not appear to affect APR exposure, but severe renal impairment increases APR exposure (AUC) by approximately 88%. Model simulations suggest a 30mg once daily dose of APR produces a drug exposure in subjects with severe renal impairment (Egfr < 30 mL/min/1.73m2 or CrCL < 30 mL/min) that is consistent with that observed in APR treated subjects given 30mg twice daily without renal impairment. The effect of mild and moderate renal impairment on the PK of APR has not been directly assessed, but the population PK analyses of 3 conditions (PsA, PSOR and RA) included a total of 86 subjects with mild (CrCL 60 - 89 mL/min; n = 77) to moderate renal impairment (CrCL 30 - 59 mL/min; n = 9).

4.2.4. Pharmacokinetics in other special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

Study CP-011 was a 2 centre, open-label, single oral dose (20 or 30mg) trial, which assessed the impact of moderate and severe hepatic impairment on the PK of APR. A total of 32 subjects were enrolled in the trial, which consisted of 8 subjects with moderate hepatic impairment (30mg dose), 8 with severe hepatic impairment (20mg dose) and 16 healthy subjects (matching doses of 20 or 30 mg). The degree of hepatic impairment was determined according to the Pugh's modification of Child's classification of severity of liver disease. Hepatic impairment subjects were matched with healthy controls of the same gender, age (+/- 5 years) and weight (+/- 13.6 kg). All doses of study medication were administered under fasting conditions. Blood samples for PK analysis (APR and M12) were collected for up to 96 hours post-dose. Study CP-011 demonstrated that moderate and severe hepatic impairment did not affect the AUC, Cmax, Tmax or T1/2 of either APR or its M12 metabolite. For each PK variable, the ratio of geometric means fell within the 90% CIs for the comparison between subjects with hepatic impairment and demographically matched control subjects.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

Study CP-019 was a 2 centre, open-label, single oral dose (30mg) trial designed to assess the PK of APR in subjects with severe renal impairment (Group 1; eGFR ≤ 30 mL/min/1.73 m2) compared with matched healthy subjects (Group 2; eGFR ≥ 90 mL/min/1.73 m2). Sixteen subjects (8 in each group) were enrolled in the study, and 15 had evaluable data. Subjects were matched with respect to age (± 15 years), gender, and weight (± 20%). Blood samples were collected for determination of APR and its major metabolite (M12) in plasma at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-dose. PK parameters were calculated from the APR plasma concentration-time data using non-compartmental methods.

In subjects with severe renal impairment (n = 7), a single 30mg dose of APR resulted in a decrease of 46.9% in apparent clearance (CL/F), and an increase in overall exposure (AUC) of 88% relative to the healthy matched subjects (n = 8) (Table 6). The AUC of M12, a pharmacologically inactive metabolite, increased by 191.7% in subjects with severe renal impairment versus healthy controls.

Table 6: Apremilast Pharmacokinetic Differences in Subjects with severe renal impairment versus Healthy Controls in Study CP-019

Group	Geometric Mean (Geometric %CV)						
	AUC_t (ng·h/mL)	AUC_∞ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
Severe renally impaired (n=8)	5333.7 (52.1)	5425.0 (53.0)	366.0 (34.5)	3 (1 – 6)	11.836 (17.6)	5.530 (52.9)	94.59 (49.3)
Matched healthy (n=7)	2848.7 (17.9)	2878.7 (17.8)	255.2 (39.7)	3 (2 – 4)	9.351 (18.1)	10.423 (17.9)	140.45 (21.8)

AUC = area under the plasma concentration-time curve; AUC_∞ = AUC from time zero extrapolated to infinity; AUC_t = AUC from time zero to the last measurable plasma concentration; CL/F = apparent total body clearance; C_{max} = Maximum plasma concentration; $t_{1/2}$ = terminal elimination half-life; t_{max} = Time to C_{max}; Vz/F= volume of distribution.

[a] t_{max} is summarized by median and range (minimum – maximum)

4.2.4.3. Pharmacokinetics according to age and gender

Study CP-024 was an open-label, parallel-group, single dose (30mg) trial evaluating the effects of age and gender on the PK of APR. The study recruited 36 subjects in total: Group 1 were aged between 65 and 85 years (n = 18; mean age of 70.5 years) and Group 2 were aged between 18 and 55 years (n = 18; mean age of 34.3 years). Subjects in Groups 1 and 2 were matched by gender and BMI. In terms of gender, there were 20 female and 16 male subjects. APR was administered under fasted conditions with 240mL of non-carbonated water at room temperature. Serial blood samples were collected prior to each dose administration and for up to 48 hours post-dose. PK parameters were calculated from plasma concentration-time data using non-compartmental methods.

After 30mg of oral APR, the median Tmax is 2.5 hours in both elderly and young subjects. Mean systemic exposure of APR as measured by AUC was slightly higher (13%) in elderly subjects compared to young subjects, however the 90% CIs for AUC crossed 100% indicating comparable exposure between young and elderly subjects within the statistical analysis. APR exhibited a T1/2 of 9 - 9.5 hours in both elderly and young subjects. Systemic exposure to APR as measured by AUC was greater in female compared to male subjects by approximately 30% (Table 7). The median Tmax was 2.75 hours in women and 2.5 hours in men. The effect of gender on AUC and Cmax was evaluated using ANOVA, and the 90% CIs for AUCt were 107-154% and for AUC∞ 109-157%, signifying statistical relevance. The T1/2 of APR was increased by 28% with reduced CL/F in female versus male subjects. The effect of age and gender was more pronounced based on a 30 - 50% higher AUC∞ in elderly females compared to that in young and elderly males, and young females.

Table 7: Apremilast Pharmacokinetic Differences by Age and Gender in Study CP-024

Age or Sex	Young N = 18	Elderly N = 18	Male N = 16	Female N = 20
PK Parameter	Geometric Mean (Geometric CV%)			
AUC_t (ng·h/mL)	2832 (28.1)	3235 (40.3)	2634 (24.5)	3382 (38.2)
AUC_∞ (ng·h/mL)	2900 (28.7)	3323 (41.8)	2673 (24.8)	3499 (39.1)
C_{max} (ng/mL)	302 (26.8)	321 (27.8)	299 (16.6)	322 (33.5)
t_{max} (h)[a]	2.50 (0.5-5.0)	2.50 (1.0-5.1)	2.50 (0.5-5.0)	2.75 (1.0-5.1)
$t_{1/2}$ (h)[a]	9.41 (2.65)	9.15 (2.56)	8.06 (1.72)	10.3 (2.76)
CL/F (L/h)	10.4 (28.7)	9.03 (41.8)	11.2 (24.8)	8.57 (39.1)
Vz/F (L)	136 (38.9)	115 (35.3)	128 (30.7)	123 (43.4)

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; CL/F = apparent total plasma clearance; C_{max} = maximum observed plasma concentration; CV% = percent coefficient of variation ; h = hour; N = number of subjects in each age/sex group; PK = pharmacokinetic; $t_{1/2}$ = estimate of the terminal elimination half-life; t_{max} = time to C_{max}; Vz/F = apparent total volume of distribution.
Elderly = Group 1 (between 65 to 85 years of age)
Young = Group 2 (between 18 to 55 years of age)
[a] Median (range) is presented for t_{max}; mean (standard deviation) is presented for $t_{1/2}$.

4.2.4.4. Pharmacokinetics according to race and ethnicity

Study CP-018 was a randomized, double-blind, PBO-controlled, 3-period, 3-sequence, 3-way crossover trial designed to assess the PK of APR in healthy Japanese, Chinese and Caucasian subjects. Japanese and Chinese subjects were age-matched (± 5 years) and BMI-matched (± 4 kg/m2) to Caucasian subjects. A total of 36 subjects were enrolled (3 groups with 12 subjects in each ethnic group) and 35 completed the study in its entirety (1 subject voluntarily withdrew due to a family emergency). Subjects received PBO, APR 20mg or APR 40mg under fasting conditions, in random order, with a washout period of 7 - 10 days between doses. Serial blood samples were collected prior to each dose administration and for up to 48 hours post-dose. PK parameters were calculated from plasma concentration-time data using non-compartmental methods.

In all 3 groups, Cmax and AUC increased in a dose proportional manner after a single oral APR dose of 20mg or 40mg. The geometric mean Cmax and AUC values were in the range of 5.55% to 19.49% less in the Japanese and Chinese subjects versus Caucasian subjects, but the magnitude of these numerical differences may be partly explained by the known between-subject APR exposure variability and the small sample size. Since the 90% CIs around the mean exposure ratios for Cmax and AUC included unity; it can be concluded that APR exposure was comparable between Japanese and Caucasian subjects, and Chinese and Caucasian subjects. In addition, there were no statistically significant differences in Tmax, CL/F and T1/2 between either Japanese and Caucasian subjects, or Chinese and Caucasian subjects.

4.2.5. Pharmacokinetic interactions

4.2.5.1. Pharmacokinetic interactions demonstrated in human studies

A total of 4 in vivo drug-drug interaction studies in humans have been performed. The results indicate that ketoconazole (Study PK-005), oral combined contraceptive pill (Study CP-020) and MTX (Study PK-010) do not have clinically significant effects on the PK of APR, and therefore, no dose adjustment for APR is necessary when it is co-administered with these drugs.

However, a potentially significant drug-drug interaction was observed in Study CP-025 with the combination of APR and rifampicin. Study CP-025 was a single centre, open-label, 3-treatment period, fixed sequence study enrolling 21 healthy young subjects (20 completed the study). The 3 study treatments included a single oral 30mg dose of APR, a single oral 30mg dose of APR followed 5 minutes later by a 30 minute infusion of 600mg of rifampicin and once daily oral

doses of 600mg rifampicin for 15 days (day 7 - 21) with a single oral 30mg dose of APR co-administered on day 20. During each study period, blood samples for PK analysis were collected prior to dosing and for up to 48 hours post-dose. PK parameters were comparable between APR alone and APR given with acute IV infusion of rifampicin. However, following treatment with multiple oral doses of rifampicin, there was a 3.6 fold increase in the mean CL/F of APR (from 10.1 L/hour to 34.5 L/hour) as well as significantly decreased AUC∞ (from 2980 ng.h/mL to 869 ng.h/mL) and Cmax values (from 331 ng/mL to 166 ng/mL). With chronic rifampicin pre-treatment for 14 days, the 90% CIs for the ratios of test versus reference for AUC∞, Cmax and CL/F were all outside the 80% - 125% bioequivalence limit. Chronic rifampicin increased the apparent clearance of APR, which resulted in a decrease in APR mean AUC∞ by 72% and reduced Cmax by 43% relative to that of APR given alone. Therefore, it can be concluded that APR exposure is decreased when administered concomitantly with strong inducers of CYP3A4, and this may result in reduced clinical response.

Study PK-005 showed that the co-administration of ketoconazole with a single 20mg dose of APR increased the mean AUC of APR by 36% and Cmax by 5%. This was single centre, open-label, non-randomized, 2-period study which recruited 18 young healthy subjects. On day 1, all subjects received a single 20mg dose of APR (given as 2 x 10mg capsules) after an 8-hour fast. Following a washout period of 5 - 7 days, subjects received a single 400mg oral dose of ketoconazole (given as 2 x 200mg tablets) each day for 7 days. On day 5 of the ketoconazole treatment period, subjects received a single 20mg dose of APR at the same time as their ketoconazole dose. Serial blood and urine samples for PK were taken pre-dose and for up to 72 hours post-dose in each of the treatment periods. Concurrent ketoconazole ingestion decreased the CL/F of APR from 9.7 L/hour to 7.1 L/hour, and increased mean AUC∞ by 36% (from 2072 h.ng/mL to 2827 h.ng/mL) and mean Cmax by 5% (from 235 ng/mL to 247 ng/mL). The 90% CI for AUC∞ was 126.2% to 147.5%, which confirmed that the co-administration of ketoconazole produces a statistically significant difference in APR exposure (based on 80% - 125% criterion). However, the sponsor asserts this is not clinically relevant based on the 50% to 200% criterion pre-defined in the study protocol. The 90% CI for Cmax was not statistically significant at 92.16% to 119.3% (based on the 80% - 125% criterion).

Study CP-020 showed that the administration of the oral contraceptive pill (OCP), Ortho Tri-Cyclen, containing ethinyl oestradiol and norgestimate, both of which are extensively metabolized by CYP3A4, does not affect APR trough concentrations. Furthermore, APR does not affect the PK exposure of both hormones. Study CP-020 was an open-label, multicentre, randomized, 2-sequence, 2-way crossover study in 40 young healthy female subjects (38 provided PK samples and 35 subjects completed the study). Following a run-in period of 28 or 56 days taking the OCP, patients were randomly assigned to either OCP for 28 days or OCP plus APR 30mg twice daily (to be taken on study days 12 - 21). Beginning on day 21 if each treatment cycle, serial blood samples were taken pre-dose and 2 hours following AM ingestion on days 19 - 22 for the determination of APR concentrations, as well as ethinyl oestradiol, norgestimate and 17-deactyl norgestimate (primary active metabolite). The PK parameters for each drug were comparable with or without co-administration of the other active medicine.

Study PK-010 showed that the co-administration of MTX with APR does not affect the PK exposure of APR, MTX and its metabolite, 7-OH MTX. In Study PK-010, multiple doses of APR were given to 15 subjects with RA (n = 12) and PsA (n = 3) who were receiving once weekly MTX (stable dose of 10 - 20 mg for at least 3 months prior). This was a multicentre, open-label, 3-treatment period, 1-sequence study. On study day 1 (treatment period 1, days 1 - 2) patients received their usual weekly dose of MTX. On days 3 - 7 (treatment period 2), subjects received APR 30mg twice daily. On days 8 - 9 (treatment period 3), patients received their usual oral MTX dose along with APR 30mg, followed by 3 additional doses of APR taken 12 hours apart. All enrolling subjects completed the entire study. Serial blood samples for the quantification of MTX and 7-OH MTX were obtained pre-dose and up to 48 hours following the AM dose in treatment periods 1 and 3. For the determination of APR concentrations, blood samples were taken pre-

dose, up to 12 hours post-dose on days 7 and 8, and a trough sample was taken on day 6. Only 1 subject each was taking a weekly dose of MTX of 10mg, 12.5mg and 17.5mg. All other subjects were taking either MTX 15mg/week (n = 6) or MTX 20 mg/week (n = 6). The PK parameters of Cmax and AUC for MTX and 7-OH MTX were comparable with or without APR co-administration. Likewise, APR concentrations reached steady state by day 7, and did not alter when MTX was co-administered.

4.2.5.2. Clinical implications of in vitro findings

Based on in vitro studies with human liver microsomes, APR did not significantly inhibit marker enzyme activities for CYP1A2, 2C9, 2C19, 2D6, 2E1 or 3A4 at the concentration evaluated. Thus, co-administration with APR is not expected to increase or decrease exposure of drugs that are substrates for these CYP enzymes. However, because APR is metabolised by CYP3A4, the sponsor conducted studies examining the potential interaction between APR and substrates for the same CYP3A4 metabolic pathway. This included 3 human PK studies: PK-005 (ketoconazole-strong CYP3A4 inhibitor), CP-025 (rifampicin-potent CYP3A4 inducer) and CP-020 (oral contraceptive pill containing ethinyl oestradiol and norgestimate, which are subject to extensive first pass metabolism via CYP3A4).

4.3. Evaluator's overall conclusions on pharmacokinetics

APR is well absorbed after oral administration with an absolute oral bioavailability of 73%, and a median time to maximal plasma concentration (Tmax) of 2.5 hours. APR demonstrates linear PK with a dose proportional increase in systemic exposure over the dose range of 10 - 100 mg daily. There is minimal accumulation of the drug when APR is administered twice daily versus once daily. Co-administration of food does not alter bioavailability.

Human plasma protein binding of APR is approximately 68%. The mean apparent volume of distribution is 87L, which is consistent with extravascular distribution. APR is extensively metabolized through hepatic cytochrome oxidative metabolism with subsequent glucuronidation, and non-CYP mediated hydrolysis. The primary pathway of metabolism is by CYP3A4 with a minor contribution from CYP1A2 and CYP2A6. APR dose not inhibit or induce CYP enzymes in vitro, suggesting that it is unlikely to have clinically significant drug-drug interactions with medicines metabolized by the CYP enzymes. Co-administration of the strong CYP3A4 inducer rifampicin resulted in a 72% reduction of APR exposure (AUC). The proposed PI recommends avoiding the concomitant use of strong CYP450 inducers with APR. In vitro data suggests that APR is a substrate and a weak inhibitor of p-glycoprotein, however in vivo data indicates that APR is unlikely to have drug-drug interactions with medicines that are inhibitors of p-glycoprotein. APR has no effect upon other drug transporter systems.

APR has an elimination half-life of 5 - 7 hours. No formal studies have been conducted in patients with mild to moderate renal impairment. However, patients with severe renal impairment are recommended to receive a reduced dose of 30mg once daily based on data in 8 subjects given a single 30mg dose of APR which resulted in the AUC and Cmax of APR increasing by 89% and 42%, respectively. No dose adjustments are recommended for patients with hepatic impairment. There is no significant impact of age and gender on APR exposure. However, subject weight (> 100 kg) may result in faster clearance and a larger volume of distribution for APR.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The pharmacodynamics (PD) of APR has been studied in 3 PSOR trials (PSOR-001, PSOR-004 and PSOR-009), 1 PsA study (PSA-002) and 1 specific QT trial (Study PK-008). None of the PD studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans.

5.2.1. Mechanism of action

APR is an inhibitor of PDE4, which works intracellularly to modulate a variety of pro- and anti-inflammatory mediators. PDE4 is cAMP specific PDE, and the dominant PDE expressed in inflammatory cells. PDE4 inhibition results in increases in intracellular cAMP, which in turn down-regulates the inflammatory response by modulating the expression of TNF, IL-17, IL-23 and other inflammatory cytokines. Elevation of intracellular cAMP also modulates anti-inflammatory cytokines (e.g. IL-10) produced by endotoxin stimulated mononuclear cells.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

5.2.2.1.1. PsA

In the Phase III Study PSA-002, a subset of 150 enrolled subjects (n = 51 in the PBO group, n = 51 in the APR 20mg arm and n = 48 in the APR 30mg group) provided blood samples for biomarker analysis at baseline, and weeks 4, 16, 24, 40 and 52. Of the 51 subjects initially randomized to PBO, 18 switched to APR 20mg twice daily and 14 switched to APR 30mg twice daily at week 16 as part of the early escape rules in the trial protocol. Rank analysis of covariance (ANCOVA) was used to compare the effect of each APR dose with PBO for the absolute change and percentage change from baseline in each of the pre-specified biomarkers. A total of 47 protein analytes were tested quantitatively using validated assays.

At week 16, statistically significant differences in the percentage change from baseline were observed with APR 30mg twice daily compared to PBO for the plasma concentrations of 7 analytes: IL-1α, IL-1β, IL-6, IL-8, TNF, ferritin (all decreased) and an increase in von Willebrand Factor (vWF). At week 24, subjects treated with either dose of APR 30mg twice daily demonstrated statistically significant differences compared to PBO in the percentage change from baseline for the plasma concentrations of the above 7 analytes plus another 3 proteins: Monocyte Chemotactic Protein-1 (MCP-1), Macrophage Inflammatory Protein-1 beta (MIP-1β) and Matrix Metalloproteinase-3 (MMP-3). For the APR 20mg twice-daily cohort, statistically significant percentage changes from baseline compared to PBO were only observed for IL-1β at week 16 and IL-2 at week 24. The changes (increase) in vWF levels with APR 30mg twice daily remained within the normal expected range of < 120 µg/mL, and the role of vWF in the pathophysiology of PsA is poorly understood. These results indicate that APR can affect several systemic inflammatory mediators, but the clinical relevance of these findings is unclear.

Logistic regression analysis was also performed to explore the relationship between the primary efficacy endpoint (modified ACR20 response) and the percentage change from baseline in biomarker concentration. Changes in TNF and vWF plasma concentrations were associated with the achievement of a modified ACR20 response at weeks 16 and 24. For vWF, the association was only significant in the APR 20mg group, and for TNF it was significant for both APR arms. However, the directionality of the association between changing median TNF levels and clinical response in the 2 APR groups was different. In the APR 20mg arm, an increase in

TNF plasma concentration was associated with a greater likelihood of achieving an ACR20 response. In contrast, patients in the APR 30mg group were more likely to achieve an ACR20 response if they had decreased TNF levels. Given PsA is an inflammatory arthritis associated with increased levels and expression of TNF, it would be expected that an effective therapy for the condition might reduce TNF plasma concentrations.

After 40 weeks of APR treatment, a total of 16 of the 47 tested analytes appeared to change compared with baseline readings. There was a significant decrease in the plasma levels of IL-6, IL-17 and IL-23 as well as an increase in IL-10 concentrations. These results indicate that APR therapy has the potential to affect several cytokines related to the Th17 pathway, which is key to the pathophysiology of PsA. The week 52 results showed a similar pattern to that observed at week 40.

5.2.2.1.2. PSOR

Study PSOR-001 was an open-label, single arm, pilot study, which enrolled 19 subjects with severe plaque PSOR and 17 completed the trial. It was conducted at 3 sites in the USA during 2005. The primary objective of the study was to evaluate the PD effects of APR (2 x 10mg tablets taken once daily upon awakening fasted; for 29 days) in reducing lesional epidermal thickness by at least 20%. Eight of the 15 subjects (53.3%) with evaluable skin biopsies demonstrated at least a 20% reduction in epidermal thickness at day 29. Epidermal thickness was reduced by a mean of 20.5% in the 15 evaluable subjects. Among the responders, T-cell numbers between baseline and day 29 were reduced by 28.8% in the dermis and 42.6% in the epidermis. Similar changes from baseline to day 29 in epidermal and dermal CD83 and CD11c cell numbers were observed. Gene expression analysis of lesional skin biopsies showed that mean mRNA expression of inducible nitric oxide synthase (iNOS) was reduced by 66.5% ($p < 0.0001$) from baseline after 29 days of APR therapy. The trial also examined the effect of APR on endotoxin-stimulated TNF expression in whole blood ex vivo. The mean decrease in lipopolysaccharide (LPS)-stimulated TNF expression 2 hours post-dose was 831.5 pg/mL after the first dose of APR, which is consistent with a statistically significant reduction in stimulated TNF.

Study PSOR-004 was a Phase II, open-label trial enrolling 30 subjects with treatment recalcitrant PSOR (20 of whom provided skin lesion biopsies at baseline [19 showed active PSOR], week 4 and week 12). Skin biopsies were analysed in 2 ways – histological response using H&E stained sections and by mRNA abundance/expression for a variety of inflammatory molecules measured by real time PCR. All patients received treatment with APR 20mg twice daily for 84 days (initial 12 week treatment phase), and there was an optional 84-day extension period whereby subjects received either APR 20mg (n = 4) or 30mg twice daily (n = 7). The study was conducted at 4 sites in the USA between August 2007 and May 2009. At week 4, the median reduction in epidermal thickness was 23.0% ($p = 0.08$ in a 2-sided Wilcoxon signed rank test) and 10 of those biopsied subjects had significant reductions in epidermal hyperplasia and Keratin 16 (K16) mRNA expression, which is a marker of keratinocyte proliferation. At week 12, the median reduction in epidermal thickness was 34.0% ($p = 0.083$) with 9 subjects showing histological improvement, including 5 with no detectable K16. In general, the reductions in K16 mRNA expression were of a higher magnitude than decreases in epidermal thickness. The study results also showed that APR produced a significant reduction in inflammatory dendritic cells (CD11c cells) and iNOS, as well as changes in pro-inflammatory gene expression (e.g. IL-23p19 and IL-17A) in PSOR lesions at weeks 4 and 12. Normalized iNOS mRNA expression was quantitatively reduced by 61% at week 4 ($p = 0.029$) and by 100% at week 12 ($p = 0.008$) in those subjects who had skin biopsies available for analysis.

The Phase III Study, PSOR-009, had a PD sub-study involving 113 subjects (41 in the PBO group and 72 in the APR 30mg twice daily group) which evaluated 47 protein biomarkers at baseline; and weeks 4, 16, 32 and 44 (i.e. similar design to the PD sub-study of PSA-002). Of the 41 subjects initially randomized to PBO, all 36 of the continuing subjects switched to APR 30mg twice daily at week 16 for the maintenance and withdrawal phases of the trial. Of the 72

subjects randomized to APR at baseline, 29 were re-randomised at week 32 (14 switched to PBO and 15 were randomized to APR again) and 19 continued without re-randomisation. Rank analysis of covariance (ANCOVA) was used to compare the effect of APR with PBO for the absolute change and percentage change from baseline in each of the pre-specified biomarkers. At week 16 (primary PD analysis time point), statistically significant differences in the percentage change from baseline were observed with APR compared to PBO for the plasma concentrations of 4 analytes: alpha 2 macroglobulin (an acute phase reactant), IL-17 (key driver of the Th-17 immune response), Chemokine Ligand 5 (CCL5) which is a keratinocyte derived chemokine over-expressed in PSOR lesions, and TIMP-1. At weeks 32 and 44, no new significant biomarker findings were identified in the PD sub-study of PSOR-009.

Furthermore, there was no significant association between changes in plasma biomarkers (at any time point) and clinical response (i.e. attainment of PASI 75).

5.2.2.2. Secondary pharmacodynamic effects

At the request of the FDA prior to commencing the Phase III studies, the effect of APR on the QT interval in healthy male subjects was investigated in Study PK-008. This was a randomized, double-blind, multiple dose, crossover trial with 4 treatments, 4 study periods and 4 treatment sequences. The primary objective was to compare APR with PBO for the time matched changes in the baseline adjusted QT interval of the ECG using an individual correction method (QTcI), as measured by the Least Square (LS) means in the treatment related difference and the largest upper 1-side 95% CI (and 2-sided 90% CIs were produced for treatment comparisons). In addition, changes from baseline in the QT interval were also analysed using Fridericia (QTcF) and Bazett (QTcB) formulae as a secondary analysis.

The study was conducted between September and December 2008 in a single USA centre. The ECG readers were blinded to treatment, sequence, time and subject identifiers. APR and matching placebo treatments were double-blinded. The 4 treatment periods requiring inpatient confinement included (1) PBO given twice daily between days 1 and 5 (total of 9 doses), (2) APR 30mg twice daily between days 1 and 5 (total of 9 doses), (3) APR 50mg twice daily between days 1 and 5 (total of 9 doses), and (4) PBO twice daily between days 1 and 4 (total of 8 doses) followed by a single 400mg dose of moxifloxacin on the morning of day 5 (open-label positive control). All study treatments were given twice daily at 8am and 8pm under fed conditions. There was a minimum 7-day wash-out period between each treatment sequence. Continuous Holter monitoring was performed between days -1 and 5 of each treatment period (i.e. for each treatment cycle, commencing at least 30 minutes prior to first drug administration and continuing for 23 hours following the day 5 morning dose). Triplicate ECG readings were extracted from the Holter monitor at various pre-specified time intervals each day (pre-dose, and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 12.0 and 23.0 hours).

The study aimed to recruit 60 young healthy male subjects (15 subjects per treatment sequence) and 53 subjects were included in the evaluable population (52 completed all 4 treatment sequences, and 1 subject completed APR 30mg and PBO). All PBO corrected, change from baseline in the LS mean QTcI values for the APR 30mg and 50mg doses were below 1ms, with the upper limit of the 2-sided 90% CI for both doses staying below 10ms at all time points. For moxifloxacin, the lower limit of the 2-sided 98% CI for each PBO corrected, change from baseline in the LS mean QTcI value was greater than 5ms for 2 - 4 hours post-dose, which is consistent with reported values for moxifloxacin. This indicates that the method used in this study had the appropriate sensitivity to detect significant change from baseline in the QTcI. The results of the secondary analyses (for both doses of APR and moxifloxacin) based on using QTcF and QTcB were similar to the results of the primary analysis derived by QTcI.

In conclusion, Study PK-008 shows that APR (up to 50mg twice daily) is not expected to produce clinically significant prolongation of the QT interval.

5.2.3. Time course of pharmacodynamic effects

Study PSA-002 demonstrated that APR treatment (30mg twice daily) resulted in statistically significant changes from baseline compared to PBO as early as week 4 for several biomarkers of interest (IL-8, MCP-1, MIP-1β, MMP-3 and TNF). The same study showed that treatment related changes from baseline in CRP became evident at week 24.

5.3. Evaluator's overall conclusions on pharmacodynamics

In both the PsA and PSOR trial programs, the biomarker analysis was exploratory in nature and designed to assess the effect of 2 doses of APR (20mg and 30mg twice daily) on a panel of 47 biomarkers associated with systemic inflammation. The PD sub-study of PSA-002 indicates that APR therapy (particularly, the 30mg twice daily regimen) may affect the plasma concentrations of several cytokines relevant to PsA, but the clinical relevance of this observation is unclear. Similarly, the PD sub-study of PSOR-009 indicates that APR therapy may affect the plasma concentrations of several cytokines relevant to PSOR, but the clinical relevance of this observation is not established.

In Studies PSOR-001 and PSOR-004, treatment with APR was associated with a decrease in dendritic cells and T-cells infiltrating skin lesions, within the epidermis and dermis. Both studies also showed a significant decrease in iNOS gene expression in skin lesion biopsies taken 2, 4 or 12 weeks after treatment initiation. In Study PSOR-001, decreased whole blood TNF expression (ex vivo) in response to endotoxin was observed 2 hours after dosing with APR. In Study PSOR-004, APR reduced lesion epidermal thickness and expression of pro-inflammatory genes and cytokines, including iNOS, IL-12/IL-23p40, IL-17A, IL-22 and IL-8. The PD results of these 2 earlier phase PSOR trials support the biological activity of APR in treating PSOR.

A well-conducted QT study (PK-008) has been performed for APR and the findings indicate no significant QTc prolongation effect was detected at the doses tested (up to 100mg daily).

6. Dosage selection for the pivotal studies

The effects of APR 20mg twice daily and APR 30mg twice daily compared with placebo (PBO) were studied in the Phase III program to assess the benefit-risk of APR in both PsA and PSOR. These doses of APR were chosen for investigation in the Phase III program based on the non-clinical and clinical pharmacology data, as well as two Phase II trials: one in PsA (Study PSA-001) and one in PSOR (PSOR-005). In vitro data and the results from early phase clinical studies (PSA-001 and PSOR-005) indicated that both the APR 20mg and 30mg twice daily doses maintained the level of APR above the half-maximal inhibitory concentration (IC50) for inhibiting the production of TNF-α, IL-2, IL-8, IL-12, interferon-gamma (IFN-γ), and MCP-1, which are key cytokines in the pathophysiology of both PsA and PSOR (Schafer et al, 2010). In addition, the 2 treatment indications have a common and overlapping target clinical population.

The Phase II Study (PSA-001) evaluated the efficacy and safety of 2 dose regimens of APR (20mg twice daily and 40mg once daily) compared with PBO over 12 weeks of treatment in adult subjects with active PsA. Separation of the modified ACR20 response rates between the active and PBO arms was seen as early as week 4 after initiation of study treatment. A statistically greater proportion of subjects in the APR 20mg twice daily treatment group versus the PBO arm achieved ACR20 (43.5% versus 11.8%, respectively; $p < 0.001$) and ACR50 responses at week 12 (17.4% versus 2.9%, respectively; $p = 0.012$). The APR 40mg once daily treatment group also achieved statistical superiority compared with PBO for the rate of ACR20 response at week 12 (35.8% versus 11.8%, respectively; $p = 0.002$), but not for the proportion of subjects achieving ACR50 response (13.4% versus 2.9%, respectively; $p = 0.056$). The safety and tolerability profile of APR was comparable between the 2 dosing groups, although the once daily regimen had more AEs leading to treatment discontinuation than the twice daily posology. Because this study

showed numerically higher ACR response rates and comparable safety, twice daily dosing of APR was selected over once daily dosing for evaluation in the Phase III PsA program.

Efficacy and safety data from the Phase II study in subjects with moderate to severe PSOR (Study PSOR-005) demonstrated a clear dose-response relationship for the studied doses (APR 10mg, 20mg and 30mg – all given as twice daily regimens). The primary endpoint of the trial was the proportion of subjects achieving a PASI 75 response at week 16. This was achieved in a statistically greater proportion of subjects in the APR 20mg and APR 30mg treatment groups (28.7% and 40.9%, respectively) versus 5.7% in the PBO arm ($p < 0.0001$ for both pair-wise comparisons). However, the APR 10mg twice daily treatment group did not record a statistically greater rate of PASI 75 response at 16 weeks compared with control (11.2%; $p = 0.1846$ for comparison versus PBO). Separation of the PASI 75 response rate between the active and PBO arms was seen at week 4 in the APR 30mg group and at week 8 in the APR 20mg arm. The safety and tolerability of APR was acceptable and comparable in both the APR 20mg and 30mg treatment groups, with no clinically significant safety signals observed at either of these doses. In addition, the APR 20mg and 30mg treatment groups displayed Cmin concentrations that exceeded the IC50 for inhibiting the production of multiple PDE4-dependant cytokines in Study PSOR-005.

Overall, given the similar pathophysiology (as well as genetic and immunologic associations) between PSOR and PsA, the sponsor has reasonably justified why it examined APR at doses of 20mg and 30mg twice daily in the Phase III study program for both treatment indications.[3] The results of Study PSA-001 supported a twice daily (versus once daily) dosing strategy with APR (both arms received a total of APR 40mg/day). The results of Study PSOR-005 demonstrated a clear dose-response relationship for APR 20mg and 30mg (both given as twice daily regimens – ie a total daily APR dose of 40-60mg).

In addition, the incidence and doses of background treatment with conventional DMARDs (mainly, MTX), CS and NSAID when used by patients in the pivotal PsA studies were appropriate, and consistent with contemporary clinical practice in Australia. Similarly, in the pivotal PSOR studies, background treatment with topical, systemic therapies and phototherapy was appropriate.

7. Clinical efficacy

7.1. Indication 1

· "Otezla is indicated for the treatment of active psoriatic arthritis in adult patients."

7.1.1. Pivotal efficacy studies

7.1.1.1. Studies PSA-002, PSA-003, PSA-004 and PSA-005

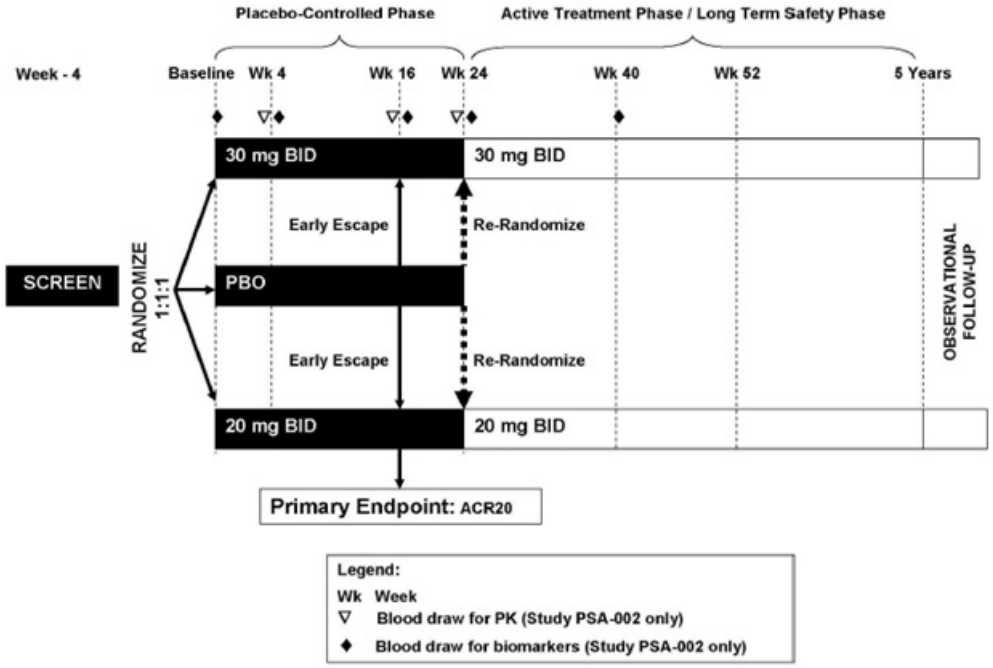
7.1.1.1.1. Study design, objectives, locations and dates

Because Studies PSA-002, PSA-003, PSA-004 and PSA-005 are highly similar in design and conduct they will be considered together in this report with their important differences highlighted and results presented independently. All of the controlled studies had 3 treatment periods preceded by a screening phase of up to 4 weeks: 1) a 24-week, randomized, double-blind, placebo-controlled phase; II) a randomized, double-blind active treatment phase of at least 28 weeks' duration, and 3) an open-label, long-term safety phase of up to 4 years' duration. In this submission, the efficacy data up to week 52 was included for Studies PSA-002, PSA-003

[3] Only the PsA indication was tested at 20 twice daily and 30 mg twice daily in Phase III studies. PSOR indication was only tested at 30mg twice daily in Phase III studies.

and PSA-004. For Study PSA-005, only the 24-week study report was available for consideration. The trial schema for the PsA studies is presented in Figure 1.

Figure 1: Study Schema for Studies PSA-002, PSA-003, PSA-004 and 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.

The design also allowed for Early Escape (EE) in patients failing to sufficiently improve. This is appropriate for ethical reasons. At week 16, subjects with < 20% improvement from baseline in both tender and swollen joint counts were eligible to enter EE in a blinded manner. Subjects in the PBO group who met EE criteria were re-randomized 1:1 to receive blinded therapy with APR 20mg twice daily or 30mg twice daily, with dose titration in the first week of active treatment. Subjects already receiving APM who met the EE criteria at week 16 continued to receive their originally assigned therapy in a blinded fashion. At week 24, all remaining subjects in the PBO cohort were re-randomized 1:1 to receive APR 20mg twice daily or 30mg twice daily, with dose titration in the first week of APR therapy.

Study PSA-005 differed from the other three Phase III studies in that it enrolled subjects who were DMARD-naïve, and any concomitant DMARDs were prohibited during the trial. Studies PSA-002, PSA-003 and PSA-004 required subjects to have been treated with conventional small-molecule and/or biologic DMARDs prior to screening, and to have inadequate response to or been intolerant of such therapies. All subjects were to have received conventional DMARD (including combination DMARDs) for at least 4 months, and were taking a stable dose for at least 4 weeks prior to screening. In Study PSA-004, all subjects were required to additionally have at least 1 qualifying PSOR lesion (≥ 2 cm in diameter) as well as active PsA.

The primary objective of the Phase III PsA study program was to demonstrate the efficacy of APR (20mg or 30mg twice daily, taken orally) on the signs and symptoms of active PsA at 16 weeks. The secondary efficacy objectives of the study program included the assessment of the effects of APR upon physical functioning indices, health related QOL and clinical disease activity (at 16, 24 and 52 weeks of treatment follow-up).

All 4 of the Phase PsA studies were conducted at multiple sites in several countries in Europe, North America and the Rest-of-World (ROW), which includes Australia, New Zealand, Korea, South Africa, Taiwan and China. The Phase III PsA study program was conducted between June

2010 and January 2013. A total of 6 protocol amendments were implemented in the Phase III PsA study program. The first amendment was instituted before the commencement of patient enrolment in Study PSA-002, and all of the other amendments occurred after. The amendments contained clarifications about baseline assessments, efficacy measures and safety related issues. None of the amendments had the potential to have impacted on the integrity of the results. However, in consideration of the design features of the pivotal Phase III studies, the timing of the primary endpoint (the modified ACR 20 response rate) was changed from week 24 to week 16 prior to database lock and data un-blinding. The sponsor states that the timing of the primary efficacy endpoint analysis at week 16 provided the only true PBO-controlled evaluation of the efficacy of APR due to EE provision at week 16 for PBO-treated patients. In addition, recent clinical trials evaluating other systemic therapies in subjects with PsA have selected primary endpoints between weeks 12 to 16 (Antoni, 2005; Mease, 2005; Kavanaugh, 2009).

7.1.1.1.2. Inclusion and exclusion criteria

To be eligible for inclusion, patients had to be at least 18 years of age with a diagnosis of PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR) of ≥ 6 month's duration in Studies PSA-002, PSA-003, and PSA-004; and ≥ 3 month's duration in Study PSA-005. In all 4 studies, subjects had to have active disease at baseline as evidenced by ≥ 3 swollen and ≥ 3 tender joints. Additionally, all subjects in Study PSA-004 had to have at least 1 qualifying PSOR lesion ≥ 2 cm in addition to active PsA. Patients with erythrodermic, guttate or generalised pustular PSOR were excluded.

The eligibility criteria for Studies PSA-002, PSA-003, and PSA-004 required subjects to have been treated with conventional small-molecule and/or biologic DMARDs. The enrolment of subjects with therapeutic failure to anti-TNF drugs was to be limited to ≤ 10% of all patients. All subjects who had been on conventional DMARD (including 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 conventional DMARD treatment with MTX (up to 25 mg/week; oral or parenteral), LEF (up to 20 mg/day), and/or SSZ (2 g/day). Concomitant treatment with biologic DMARD was prohibited, and all of these agents must have been ceased at least 12 weeks prior to baseline. Subjects who had previously failed treatment with > 3 agents for PsA (sum of conventional and/or biologic DMARDs) or >1 anti-TNF drug were excluded. The eligibility criteria for Study PSA-005 differed from the other three Phase III studies in that it enrolled subjects who were DMARD-naïve, and any concomitant DMARDs (including MTX, LEF, and SSZ) were prohibited during the trial.

In all four Phase III studies, the concomitant use of oral CS was permitted for subjects taking stable doses (prednisone [or equivalent] < 10 mg/day) for at least 1 month prior to screening. The dose of CS was to remain stable up to week 52. Concomitant NSAID and narcotic analgesia was also permitted, provided subjects were on a stable dose for at least 2 weeks prior to screening. Changes to NSAIDs due to toxicity were permitted between weeks 24 and 52. Low potency topical CS were allowed as background therapy for PSOR affecting the face, axillae and groin; and subjects with scalp PSOR were allowed to use coal tar and/or salicylic acid preparations.

Co-morbid conditions were an exclusion criterion based on investigator decision as to their clinical significance (including cardiac, pulmonary, neurologic, psychiatric and any major uncontrolled disease). A past history of substance abuse within the last 6 months, infection requiring treatment within 4 weeks of screening, major surgery within 8 weeks prior to screening (or planned within 6 months following randomisation) and a history of an infected joint prosthesis at any time were to be excluded. A history of malignancy (except for excised basal or squamous cell skin cancers, or cervical carcinoma in situ successfully treated by surgery) was also an exclusion criterion.

Subjects were screened for Hepatitis B and C, as well as HIV infection at baseline, but not routinely tested for latent Tuberculosis (TB) apart from requiring a chest X-ray to have been taken within 12 weeks prior to screening. Subjects with active TB or a history of incompletely treated TB were excluded. Subjects with significant laboratory abnormalities at screening and baseline were excluded. This included serum transaminases > 2 x Upper Limit Normal (ULN), total serum bilirubin > 34 µmol/L, serum creatinine > 1.5 mg/dL, total white blood cell count < 3.0 x 109/L or > 14.0 x 109/L, platelet count < 100 x 109/L, haemoglobin < 9.0 g/dL and haemoglobin A1c > 9.0%. A clinically significant abnormality on 12 lead ECG at screening was also an exclusion criterion.

7.1.1.1.3. Study treatments

Following randomisation, APR was dose-titrated in 10 mg/day increments over the first week of treatment to limit gastrointestinal AEs. In accordance with the titration schedule proposed by the sponsor in this submission, subjects in the APR 20mg twice-daily treatment groups reached their target dose on day 4, and subjects in the APR 30mg twice-daily treatment arms reached their target dose on day 6.

In Studies PSA-002, PSA-003 and PSA-004, all subjects who had been on conventional DMARD at baseline were required to continue treatment without dose modification through the end of the PBO-controlled phase (week 24) with MTX (up to 25 mg/week; oral or parenteral), LEF (up to 20 mg/day), and/or SSZ (2 g/day). One DMARD dose reduction was permitted between weeks 24 and 52. In all four Phase III studies, the concomitant use of oral CS was permitted for subjects taking stable doses (prednisone [or equivalent] < 10 mg/day) for at least 1 month prior to screening. The dose of CS was to remain stable up to week 52. Concomitant NSAID and narcotic analgesia was also permitted, provided subjects were on a stable dose for at least 2 weeks prior to screening. Changes to NSAIDs due to toxicity were permitted between weeks 24 and 52.

7.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables relevant to the PsA submission were the modified American College of Rheumatology (ACR) response criteria; and the HAQ (Health Assessment Questionnaire) - Disability Index (DI). An understanding of these endpoints will help the interpretation of the results.

The primary efficacy outcome in all 4 of the Phase III PsA studies was the proportion of subjects achieving the modified ACR20 response at week 16. This endpoint is appropriate for evaluating the effect of treatment on the signs and symptoms of PsA. The ACR response criterion is a composite endpoint, which quantifies the clinical response to therapy in patients with RA and PsA. The ACR criteria have been modified for PsA subjects by the addition of the DIP joints of the toes and the carpometacarpal joints (these joints are not included in the ACR response criteria for RA). A PsA patient with an ACR20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen (maximum of 76) and tender (maximum of 78) joint counts, as well as a 20% improvement in any 3 of the 5 core-set measures which include Patient's Global Assessment of disease activity (PtGA), Physician's Global Assessment of disease activity (PhGA), Patient's Assessment of Pain score (on 10 cm VAS), Patient's assessment of physical function as measured by the HAQ-DI, and acute phase reactants (CRP). The ACR50 and ACR70 levels of response are calculated using the same criteria as the ACR20, but with a higher percentage improvement (50% and 70%, respectively) instead of 20%.

The key secondary endpoint in the Phase III PsA studies was the LS (least square) mean change from baseline to week 16 in the HAQ-DI score. The HAQ-DI is a validated method for measuring disability in inflammatory arthritis (range: 0 - 3 with higher score indicating more functional impairment). It assesses physical function by measuring the patient's ability to perform the following 8 activities (using 20 questions): -dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity. The measure uses a scale ranging from zero (best) to three

(worst). The minimal clinically important difference (MCID) for the HAQ-DI score for patients with PsA has not been fully established but most clinicians consider a change in the HAQ-DI of -0.30 units to be the best validated cut-off threshold (Mease et al, 2011). However, other authors have suggested a much lower threshold of change (-0.13 units) as being acceptable (Kwok et al, 2010). The sponsor has nominated both thresholds of HAQ-DI score change (-0.13 and -0.30 units) as the MCID in the Phase III PsA trials, but in this report only data for the higher level of MCID will be presented as this is the best validated cut-off threshold.

There was a very large number of other secondary efficacy outcomes (grouped below by disease manifestation/category) assessed at weeks 24 and 52, which included:

- Proportion of patients achieving ACR20/50/70 response,
- Physical Function - Proportion of subjects with HAQ-DI response,
- Other clinical features of PsA – Proportion of patients achieving Psoriatic Arthritis Response Criteria (PsARC), CDAI and EULAR response; as well as the mean change from baseline in enthesitis and dactylitis scores,
- Skin Effects – proportion of subjects with PASI 75 response, and
- Heath-related outcomes – Mean change from baseline in SF-36, FACIT-F and DLQI scores.

Enthesitis was assessed using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), which assesses 13 core axial sites (e.g. proximal insertion of the Achilles tendons) in a dichotomous 0/1 score for tenderness. The index has a score range of 0 - 13. The presence and severity of dactylitis was assessed in both hands and feet (n = 20 digits) using a dichotomous scoring system for each site (with 0 = not present and 1 = present). The dactylitis score has a range from 0 - 20. There is no validated acceptance of what constitutes the MCID in enthesitis and dactylitis score.

The Psoriatic Arthritic Response Criteria (PsARC) contains a variation of 4 of the measures of the ACR20 response (swollen and tender joint counts; as well as the PhGA and PtGA) but does not include a measure of pain, function/disability, or an acute phase reactant (CRP). PsARC response is defined as no worsening in any of the criteria listed below, and an improvement from baseline in at least 2 of the following 4 criteria, one of which has to be either the tender or swollen joint count:

- PhGA - decrease by 1 point in the 5-point Likert scale,
- PtGA - decrease by 1 point in the 5-point Likert scale,
- Tender Joint Count - at least 30% improvement in the 78 joint count, and
- Swollen Joint Count - at least 30% improvement in the 76 joint count.

Worsening of criteria is defined as >20% increase for global assessments, and > 30% increase for joint counts.

The 28 joint Disease Activity Score (DAS28) is a widely used and validated method used in research trials and clinical practice for measuring outcome in patients with RA and PsA. It is a composite disease activity index of 4 clinical variables involving the tender joint count (up to 28 joints), swollen joint count (up to 28 joints), CRP and the PtGA. The final score is derived by a complex mathematical calculation of the individual elements. DAS28 has a scale from 0 to 10, and most scores range from around 2 to a maximum of 10. According to EULAR guidelines, DAS28 > 5.1 indicates high disease activity, < 3.2 indicates low disease activity, and clinical remission is indicated by a DAS28 score of < 2.6. The European League Against Rheumatism (EULAR) response criteria classify each subject as a good, moderate, or non-responder to treatment based on the degree of improvement from baseline and the level of disease activity at the endpoint. EULAR response is derived using the individual subject's DAS28 score. A good

EULAR response is defined as DAS28 ≤ 3.2 and improvement from baseline > 1.2. Moderate EULAR response is DAS28 score > 3.2 and improvement from baseline > 1.2, or DAS28 ≤ 5.1 with improvement from baseline > 0.6 but ≤ 1.2.

The Clinical Disease Activity Index (CDAI) is another composite index that is not dependant on the results of acute phase reactant testing. The CDAI score ranges from 0 to 76, and the following thresholds of disease activity have been defined for the CDAI: remission is ≤ 2.8, low disease activity is > 2.8 and ≤ 10, moderate disease activity is > 10 and ≤ 22, and high disease activity is a score > 22.

The Psoriasis Area and Severity Index (PASI) is an assessment of 4 anatomic sites (head, upper extremities, trunk, and lower extremities) for erythema, induration, and desquamation using a scale of zero (the best evaluation, no symptoms) to four (the worst evaluation, very marked). The extent of lesions in a given area is assigned a numerical value from one (< 10%) to six (90-100%). The PASI score is then calculated from a weighted average based on the % of body surface area (BSA) of the anatomic site (head, 10%; upper extremities, 20%; trunk, 30%; and lower extremities, 40%). The PASI score has a range from 0 (no disease) to 72 (maximal disease), and responses can be based on at least 50%, 75%, 90% and 100% improvement in scores from baseline. The PASI 50 response is generally considered the MCID (Caitlin et al, 2004).

The SF-36 (version 2) is a generic health assessment questionnaire intended to measure general health concepts not specific to any age, disease, or treatment group. This instrument has been validated in patients with PsA. It measures 8 health domains: Physical Functioning (PF; 10 questions), pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems. It also can be subdivided into two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores. An improvement of > 5 points in the PCS or MCS is defined as a clinically meaningful improvement.

The DLQI is a 10-item questionnaire developed as a measure of disability for a wide range of dermatological conditions. It assesses the patient's perspective on the impact of skin disease on daily living. The DLQI has 4 item response options (0 - 3) with the total score ranging from 0 - 30 (higher score indicates greater impact of skin disease upon daily living). An overall score of 0 - 1 indicates no effect on the patient's life, 2-5 equals small effect, 6 - 10 indicates moderate impact, 11 - 20 is consistent with large effect and 21 - 30 represents an extremely large impact. The DLQI has been validated in the assessment of PSOR, and shows discrimination and responsiveness in PsA trials as well.

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F; version 4) scale is a 13-item, self-administered questionnaire that assesses both the physical and functional consequences of fatigue. Each question is scored from 0 to 4. The total FACIT-Fatigue score ranges from 0 to 52, with higher scores denoting lower levels of fatigue. An MCID for improvement in the FACIT-Fatigue has not been validated for PsA patients.

7.1.1.1.5. Randomisation and blinding methods

The IVRS stratified the randomization according to DMARD treatment (yes/no) and ensured that at least 25 subjects in the DMARD treated subgroup of each investigational arm were taking either LEF or SSZ.

Placebo subjects who did not experience at least 20% improvement in tender and swollen joint counts by week 16 (i.e. met EE criteria) were required to switch over to active treatment with APR - re-randomized 1:1 in a blinded fashion to either 20mg or 30mg twice daily. Subjects on APR who met the EE criteria continued to receive, in a blinded fashion, the same dose of APR to which they were originally assigned. After 24 weeks, all subjects in the PBO group who had not entered EE at week 16 were to be re-randomized 1:1 to receive 20mg or 30mg twice daily of APR, stratified for concomitant DMARD use (yes/no). Subjects who were receiving APR from the

start until week 24 continued to receive their randomized APR treatment in a blinded manner thereafter until week 52.

For Studies PSA-002, PSA-003 and PSA-004, treatment assignments were stratified based on conventional DMARD use at baseline (yes/no) and in Study PSA-004, additionally by baseline PSOR BSA involvement (< 3% and ≥ 3%). In the DMARD stratum of each treatment group, at least 25 subjects were to be taking either LEF or SSZ.

In each of the 4 Phase III PsA studies, eligible subjects were randomized 1:1:1 to receive APR 20mg twice daily, APR 30mg twice daily or identically appearing placebo tablets during the 24-week placebo-controlled phase. Blinding was maintained by the use of identical blister cards for all subjects.

7.1.1.1.6. Analysis populations

Efficacy analyses were conducted using 3 analysis populations. The Full Analysis Set (FAS) was the primary population for the analyses of efficacy during the placebo-controlled period (weeks 0 - 24). The FAS consisted of all subjects who were randomized as specified in the protocol. Subjects who were randomized in error and did not receive any dose of study drug (APR or placebo) were excluded from FAS. However, any subjects who were randomized in error but did receive at least 1 dose of study drug (APR or placebo) were to be included in the treatment group to which they were randomized. For the analyses using the FAS, subjects were included in the treatment group to which they were randomized, irrespective of the treatment actually received.

The Per-Protocol (PP) population was used for supportive analyses of efficacy during the placebo-controlled period (weeks 0 - 24), namely for sensitivity analyses performed for the primary endpoint (i.e. the rate of modified ACR20 response at week 16) and the major secondary endpoint (change from baseline in the HAQ-DI score at week 16). The PP population included all subjects who were randomized, received at least 1 dose of study medication, and who had at least 1 change from baseline in the TJC or SJC as well as at least 3 of the other 5 ACR components (i.e. they were able to be assessed for ACR response). In addition, PP subjects had to have no critical protocol violations that could have substantially affected the results of these endpoints. For the analyses using the PP population, subjects were included in the treatment group to which they were randomized.

The third analysis group definition was the APR Subjects as Initially Randomized/Re-randomized (AAR) population. This was used for the analyses of efficacy during the APR-exposure period up to week 52. The AAR population consisted of all subjects who were randomized or re-randomized to receive APR at any time during the study (i.e. subjects randomized to an APR treatment group at week 0, subjects initially randomized to placebo who entered EE and were re-randomized to APR at week 16, and subjects initially randomized to placebo who completed 24 weeks of treatment on placebo and, as per the protocol, were re-randomized to APR at week 24). For the analyses using the AAR Population, subjects were included in the treatment group to which they were randomized or re-randomized, irrespective of APR dosing regimen they received.

In the AAR Population analyses, subjects originally randomized to placebo are represented in the PBO/20 EE, PBO/30 EE, PBO/20 XO, and PBO/30 XO treatment groups, depending on whether they were re-randomized to APR as part of early escape at week 16 (EE groups) or at week 24 as per the crossover protocol (XO groups). The size of these treatment groups is smaller than the original APR 20 mg and 30mg treatment groups. Subjects who were initially randomized to placebo and discontinued from the study prior to week 16 were not accounted for in these treatment groups, as those subjects were never re-randomized to receive APR. The AAR population analyses also included the subsets of subjects initially randomized to APR who entered early escape (APR 20/30 EE) or who completed week 16 and did not enter early escape (APR 20/30 NEE). Subjects who were initially randomized to APR, but discontinued prior to

week 16, are not included in the EE or NEE groups, as early escape status for these subjects cannot be determined. Therefore, the sum of the EE + NEE subsets does not comprise the total APR 20/30 populations.

7.1.1.1.7. Sample size

Sample size calculations for each of the 4 pivotal Phase III PsA trials were based on the results of the Phase II study (PSA-001). A 2-group chi-square test with a 0.025 2-sided significance level would have more than 95% power to detect an absolute treatment related difference of 20% (40% versus 20%) between 1 dose regimen of APR and PBO for the proportion of subjects achieving a modified ACR20 response, when the sample size in each treatment group was 165.

7.1.1.1.8. Statistical methods

The primary efficacy endpoint in all of the 4 pivotal PsA studies was the modified ACR20 response rate at week 16. The proportion of subjects who were randomized to APR (20mg or 30mg twice daily) or PBO who achieved this outcome was compared using a chi-square test. Subjects who discontinued from the studies before week 16, or who had insufficient data for assessment at week 16 were considered as non-responders (i.e. Non-Responder Imputation [NRI] approach). The Last Observation Carried Forward (LOCF) methodology was used an alternative approach to handle missing data in the sensitivity analyses. In each study, the Hochberg procedure was used to maintain the Type 1 error at the 0.05 significance level. Pair-wise comparisons of APR 30mg versus PBO, and APR 20mg versus PBO were performed. The results of the endpoint were to be considered statistically significant if both doses of APR versus PBO were statistically significant at the 0.05 significance level or if one of the comparisons was statistically significant at the 0.025 level.

The key secondary efficacy endpoint was the effect of APR on physical functioning as measured by HAQ-DI. The mean change in HAQ-DI score at week 16 in reference to baseline was compared using analysis of covariance (ANCOVA) on the change from baseline, with treatment as a factor in the model and the baseline HAQ-DI score as the covariate. Pair-wise treatment comparisons of APR 30mg versus PBO and APR 20mg versus PBO were to be conducted conditional on observing positive results for the primary efficacy endpoint. Specifically, if the ACR20 primary endpoint was statistically significant for both APR dose groups, then the pair-wise comparisons for the HAQ-DI were to be evaluated using the Hochberg procedure at the 0.05 level. However, if the primary efficacy endpoint was statistically significant for only one of the APR dose groups, then the HAQ-DI was only to be evaluated for that dose level using the 0.025 significance level.

The other secondary efficacy endpoints were to be analysed in a sequential order only if the ACR20 and HAQ-DI endpoint were statistically significant. The Hochberg procedure was used to adjust for multiple comparisons. For the week 24 analyses, subjects who met the EE criteria were to be counted as non-responders. The sequential order of secondary efficacy endpoint testing following the mean change from baseline to week 16 in HAQ-DI score was:

- ACR20 response rate then HAQ-DI change (both at week 24) followed by
- Change from baseline to week 16 (in order) – SF-36 physical function score, PsARC response rate, MASES score, dactylitis score, CDAI change, DAS28 (CRP) remission rate and FACIT-F score; then
- Change from baseline to week 24 (in order) - SF-36 physical function score, PsARC response rate, MASES score, dactylitis score, CDAI change, DAS28 (CRP) remission rate and FACIT-F score.

7.1.1.1.9. Participant flow

Each of the Phase III studies will be presented independently but Table 8 provides a summary of subject disposition in Studies PSA-002, PSA-003 and PSA-004 at weeks 16 and 24. As expected,

a greater number of PBO treated subjects entered EE at week 16 compared to APR treated subjects. At week 16, a slightly higher number of APR 30mg treated subjects in Studies PSA-002 and PSA-003 discontinued due to AEs compared to subjects in the PBO arm and those treated with APR 20mg twice daily. Discontinuation due to lack of efficacy was similar among the treatment groups.

Table 8: Subject Disposition at Weeks 16 and 24 in Studies PSA-002, PSA-003 and PSA-004

	Number (%) of Subjects								
	PSA-002			PSA-003			PSA-004		
Subjects who:	Placebo N = 168	APR 20 BID N = 168	APR 30 BID N = 168	Placebo N = 159	APR 20 BID N = 163	APR 30 BID N = 162	Placebo N = 169	APR 20 BID N = 169	APR 30 BID N = 167
Received at least 1 dose of IP	168 (100.0)	168 (100.0)	168 (100.0)	159 (100.0)	163 (100.0)	162 (100.0)	169 (100.0)	169 (100.0)	167 (100.0)
Completed Week 16 visit	**158 (94.0)**	**158 (94.0)**	**154 (91.7)**	**148 (93.1)**	**151 (92.6)**	**149 (92.0)**	**156 (92.3)**	**157 (92.9)**	**156 (93.4)**
Discontinued prior to Week 16	10 (6.0)	10 (6.0)	14 (8.3)	11 (6.9)	12 (7.4)	13 (8.0)	13 (7.7)	12 (7.1)	11 (6.6)
Primary reason for discontinuation									
Adverse event	5 (3.0)	5 (3.0)	9 (5.4)	3 (1.9)	4 (2.5)	11 (6.8)	6 (3.6)	6 (3.6)	5 (3.0)
Lack of efficacy	3 (1.8)	2 (1.2)	2 (1.2)	2 (1.3)	2 (1.2)	0	2 (1.2)	3 (1.8)	2 (1.2)
Noncompliance with study drug	0	0	1 (0.6)	0	0	0	0	0	0
Withdrawal by subject	1 (0.6)	1 (0.6)	2 (1.2)	5 (3.1)	5 (3.1)	1 (0.6)	2 (1.2)	3 (1.8)	1 (0.6)
Death	0	1 (0.6)	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	1 (0.6)	0	0	0	0	1 (0.6)
Protocol violation	1 (0.6)	0	0	0	0	1 (0.6)	0	0	1 (0.6)
Other	0	1 (0.6)	0	0	1 (0.6)	0	3 (1.8)	0	1 (0.6)
Early escaped at Week 16	107 (63.7)	78 (46.4)	58 (34.5)	88 (55.3)	59 (36.2)	64 (39.5)	97 (57.4)	76 (45.0)	53 (31.7)
Completed the Placebo-Controlled Phase (Week 24 visit)	**150 (89.3)**	**146 (86.9)**	**148 (88.1)**	**143 (89.9)**	**143 (87.7)**	**142 (87.7)**	**146 (86.4)**	**147 (87.0)**	**145 (86.8)**
Week 24 completion rate among non-EE subjects, n/N (%)[a]	48/61 (78.7)	74/90 (82.2)	90/110 (81.8)	57/71 (80.3)	87/104 (83.7)	78/98 (79.6)	50/72 (69.4)	71/93 (76.3)	93/114 (81.6)
Week 24 completion rate among EE subjects, n/N (%)[b]	102/107 (95.3)	72/78 (92.3)	58/58 (100.0)	86/88 (97.7)	56/59 (94.9)	64/64 (100.0)	96/97 (99.0)	76/76 (100.0)	52/53 (98.1)

7.1.1.1.9.1. Study PSA-002

In Study PSA-002, a total of 615 subjects were screened for inclusion, of which 504 (168 in each of the 3 treatment groups) were randomised and included in the FAS at 83 study sites. The most frequent reasons for screen failure (18.0% in total; 111/615) were not meeting safety blood test requirements (3.4%; 21/615), failure to meet protocol requirements (3.3%; 20/615) and active joint counts < 3 at baseline (2.8%; 17/615).

A total of 93.3% (470/504) of subjects continued until the week 16 assessment at a similar frequency in each of the 3 treatment groups: 94.0% (158/168) in the PBO and APR 20mg treatment groups, and 91.7% (154/168) in the APR 30mg arm. The most frequent reasons for discontinuation were AEs (19 subjects) and lack of efficacy (7 subjects), both of which occurred at similar frequencies in each of the 3 treatment groups. The proportion of subjects who entered EE at week 16 was higher in the PBO group (63.7%; 107/168 – 54 switched to APR 20mg and 53 switched to APR 30mg twice daily) and decreased in a dose dependent manner in the APR treatment groups (46.4% [78/168] in the 20mg group and 34.5% [58/168] in the 30mg dose arm).

Overall, 88.1% (444/504) of subjects completed the PBO controlled period (weeks 0 - 24): 89.3% (150/168) in the PBO group, 86.9% (146/168) in the APR 20mg arm and 88.1% (148/168) in the APR 30mg group. AEs (24 subjects), lack of efficacy (11 patients) and withdrawal of consent (10 subjects) were the most common reasons for study cessation up to week 24. In the 107 PBO to APR EE switch subjects (week 16), 5 patients discontinued before 24 weeks, 4 of which were due to AEs and 1 because of lack of efficacy.

The majority of patients (96.4%; 428/444) who completed the PBO controlled phase (first 24 weeks) entered into the active treatment extension period, and 87.1% (373/428) completed until week 52. The rate of completion at 52 weeks among subjects initially randomized to APR was 73.8% (118/168) in the 20mg group and 77.4% (121/168) in the 30mg arm. Additionally, 70.8% (119/168) of patients randomized to PBO completed until week 52 (including 44/54 in the PBO/20 EE group, 34/53 in the PBO/30 EE arm, 19/23 in the PBO/20 crossover group and 22/24 in the PBO/30 crossover cohort).

7.1.1.1.9.2. Study PSA-003

In Study PSA-003, a total of 611 subjects were screened for involvement, and 488 were randomized at 84 centres. Four subjects were randomized in error and did not receive any investigational drug. As such, 484 subjects were included in the FAS: 159 in the PBO group, 163 in the APR 20mg arm and 162 patients in the APR 30mg treatment group. The reasons for screen failure in Study PSA-003 were similar in nature and frequency to Study PSA-002.

At week 16, 92.6% (448/484) were still involved in the trial: 93.1% (148/159) in the PBO group, 92.6% (151/163) in the APR 20mg arm and 92.0% (149/162) in the APR 30mg arm. The most frequent reasons for discontinuation were AEs (18 subjects; 11 of which were in the APR 30mg group) and withdrawal by subjects (11 subjects; 5 each in the PBO and APR 20mg groups). The proportion of subjects who entered EE at week 16 was higher in the PBO group (55.3%; 88/159 – 44 in each of the APR dose switch groups) compared to those initially randomised to APR therapy (36.2% [59/163] in the 20mg group and 39.5% [64/162] in the 30mg dose arm).

A total of 428 subjects (88.4% of 484) completed the PBO controlled period (weeks 0 - 24): 89.9% (143/159) in the PBO group, and 87.7% in each of the APR treatment arms (143/163 in the 20mg group and 142/162 in the 30mg arm). In the 88 patients who switched from PBO to APR via EE at 16 weeks, 4 patients discontinued before 24 weeks, 1 due to AE and 1 because of lack of efficacy.

The majority of patients (95.8%; 410/428) who completed the PBO controlled phase (first 24 weeks) entered into the active treatment extension period, and 88.0% (361/410) completed until week 52. The rate of completion at 52 weeks among subjects initially randomized to APR was 76.7% (125/163) in the 20mg group and 70.4% (114/162) in the 30mg arm. Additionally, 76.7% (122/159) of patients randomized to PBO completed until week 52 (including 35/44 in the PBO/20 EE group, 34/44 in the PBO/30 EE arm, 25/27 in the PBO/20 crossover group and 28/28 in the PBO/30 crossover cohort).

7.1.1.1.9.3. Study PSA-004

A total of 612 subjects were screened for enrolment in this study, of whom 505 were randomized and treated in Study PSA-004 (78 sites): 169 subjects in the PBO group, 169 patients in the APR 20mg arm and 167 subjects in the APR 30mg group. The reasons for screen failure in Study PSA-004 were similar in nature and frequency to Study PSA-002.

A total of 469 (92.9% of 505) subjects completed study involvement up until week 16 at a comparable frequency between the treatment groups: 92.3% (156/169) in the PBO group, 92.9% (157/169) in the APR 20mg arm and 93.4% (156/167) in the APR 30mg arm. The most frequent reasons for discontinuation were AEs (17 subjects) and lack of efficacy (7 subjects). The proportion of subjects who entered EE at week 16 was higher in the PBO group (57.4%; 88/159 – 47 switched to APR 20mg and 50 switched to APR 30mg twice daily) and decreased in a dose dependent manner in the APR treatment groups (45.0% [76/169] in the 20mg group and 31.7% [53/167] in the 30mg dose arm).

Overall, 86.7% (438/505) of subjects completed the PBO controlled period (weeks 0-24): 86.4% (146/169) in the PBO group, 87.0% (147/169) in the APR 20mg arm and 86.8% (145/167) in the APR 30mg group. AEs (19 subjects) were the most common reason for study

discontinuation up to week 24. In the 97 PBO to APR EE switch subjects (week 16), only 1 patient discontinued before 24 weeks (for lack of efficacy).

The majority of patients (95.2%; 417/438) who completed the PBO controlled phase (first 24 weeks) entered into the active treatment extension period, and 88.2% (368/417) completed until week 52. The rate of completion at 52 weeks among subjects initially randomized to APR was 71.0% (120/169) in the 20mg group and 75.4% (126/167) in the 30mg arm. Additionally, 72.2% (122/169) of patients randomized to PBO completed until week 52 (including 32/43 in the PBO/20 EE group, 44/50 in the PBO/30 EE arm, 23/25 in the PBO/20 crossover group and 23/25 in the PBO/30 crossover cohort).

7.1.1.1.9.4. Study PSA-005

In Study PSA-005, a total of 658 subjects were screened for inclusion, of which 528 were randomised (99 sites). One subject in the APR 30mg cohort was randomised in error and did not receive any study treatment. This individual was excluded from the FAS and therefore 527 subjects were included in the efficacy analysis cohort: 176 subjects in the PBO group, 175 in the APR 20mg arm and 176 in APR 30mg treatment group. At week 16 (time point for assessing the primary efficacy endpoint), the majority of subjects completed follow-up in similar proportions in each group: 94.3% (166/176) in the PBO group, 96.0% (168/175) in the APR 20mg arm and 94.3% (166/176) in the APR 30mg group. The most frequent reasons for discontinuation before week 16 were subject withdrawal (12 subjects in total) and AEs (9 subjects), both of which occurred at similar frequencies in each of the 3 treatment groups. The proportion of subjects who entered EE at week 16 was higher in the PBO group (58.5%; 103/176 – 51 switched to APR 20mg and 52 switched to APR 30mg twice daily) compared to the 2 original APR treatment groups (41.7% [73/175] in the 20mg group and 44.9% [79/176] in the 30mg dose arm).

At total of 471 subjects completed up to week 24: 88.6% (156/176) in the PBO group (including EE switch subjects), 91.4% (160/175) in the APR 20mg arm and 88.1% (155/176) in the APR 30mg cohort. Withdrawal of subjects and AEs remained the most common reasons for study cessation up to week 24. In the 103 PBO to APR EE switch subjects, only 1 patient in the 20mg arm discontinued before 24 weeks and this was due to an AE.

7.1.1.1.10. Major protocol violations/deviations

7.1.1.1.10.1. Study PSA-002

A total of 15 subjects (3.0% of 504) were excluded from the FAS because of protocol deviations, which had the potential to impact upon efficacy assessments. This included 3 subjects in the PBO group, 5 in the APR 20mg arm and 8 in the APR 30mg group. The main reasons for exclusion from the PP cohort were missing baseline or post-baseline ACR component data, and insufficient study drug adherence.

During the 24 week PBO controlled period, 12.1% (61/504) of subjects had at least 1 protocol violation recorded. The most common protocol violations across all treatment groups were failure to meet inclusion/exclusion criteria (4.6%; 23/504) and taking of excluded medication (3.0%; 15/504). Between weeks 24 and 52, 3 patients (0.7% of 428) had at least 1 reported protocol violation.

7.1.1.1.10.2. Study PSA-003

Overall, 20 subjects (4.1% of 484) were excluded from the FAS because of protocol deviations, which had the potential to impact upon efficacy assessments. This included 5 subjects in the PBO group, 4 in the APR 20mg arm and 11 in the APR 30mg group. The main reasons for exclusion from the PP cohort were missing baseline or post-baseline ACR component data, and insufficient study drug adherence.

During the 24 week PBO controlled period, 26.0% (126/484) of subjects had at least 1 protocol violation recorded. The most common protocol violations across all treatment groups were

informed consent issues (9.7%; 47/484), failure to perform protocol specified procedures or assessments (7.9%; 38/484) and taking of excluded medication (5.2%; 25/484). Between weeks 24 and 52, 5 patients (1.2% of 410) had at least 1 reported protocol violation.

7.1.1.1.10.3. Study PSA-004

A total of 19 subjects (4.6% of 505) were excluded from the FAS because of protocol deviations, which had the potential to impact upon efficacy assessments. This included 5 subjects in the PBO group, 6 in the APR 20mg arm and 8 in the APR 30mg group. The main reason for exclusion from the PP cohort was missing baseline or post-baseline ACR component data (16/19 subjects).

During the 24 week PBO controlled period, 14.9% (75/505) of subjects had at least 1 protocol violation recorded. The most common protocol violations across all treatment groups were failure to perform protocol specified procedures or assessments (7.5%; 38/505) and taking of excluded medication (5.3%; 27/505). Between weeks 24 and 52, 4 patients (1.0% of 417) had at least 1 reported protocol violation.

7.1.1.1.10.4. Study PSA-005

In total, 4.9% (26/527) of subjects were excluded from the FAS because of protocol deviations which had the potential to impact upon efficacy assessments. Overall, 501 subjects (166 in the PBO group, 168 in the APR 20mg arm and 167 in the APR 30mg group) were included in the PP population. The main reason for exclusion from the PP cohort was missing baseline or post-baseline ACR component data, which occurred at a similar frequency in each of the treatment groups.

Overall, at least 1 protocol violation was recorded in 7.8% (41/527) of subjects in the FAS. The most common protocol violation across all treatment groups was a failure to perform protocol specified procedures or assessments (5.9%; 31/527).

7.1.1.1.11. Baseline data

7.1.1.1.11.1. Study PSA-002

The majority of subjects enrolled in this trial were Caucasian (90.3%; 455/504) and just over half (50.6%; 255/504) were female. Overall, patients had a mean age of 50.4 years (range: 19 - 83 years), and 10.3% (52/504) of all subjects were aged 65 years or older. The mean BMI of the enrolled cohort was 30.86 kg/m2, and half of all subjects (50.8%; 256/504) had a BMI < 30 kg/m2. By geographic region, subjects came from North America (44.2%; 223/504), ROW countries (31.5%; 159/504) and Europe (24.2%; 122/504). The 3 treatment groups were well matched at baseline for demographic characteristics, although the APR 30mg group had a greater percentage of female subjects (54.8%; 92/168) than the other 2 treatment arms (47.6% [80/168) in the PBO group and 49.4% [83/168] in the APR 20mg arm).

The treatment groups were similar with respect to baseline PsA features. The mean duration of PsA for all subjects was 7.53 years (median 5.05 years, range: 0.5 - 40.7 years). The predominant subtypes of PsA were symmetrical polyarthritis (63.5%; 320/504) followed by asymmetrical oligoarthritis (26.0%; 131/504). Nearly all subjects (99.4%; 501/504) had a confirmed diagnosis of PSOR with a median duration of 13.1 years. The mean PASI score was 8.54 (median 5.30), and just less than half of subjects (45.0%; 306/504) had at least 3% BSA involvement at baseline.

In terms of PsA disease activity at baseline, the mean numbers of tender and swollen joints were similar for all 3 treatment groups at 22.2 - 23.3 and 12.5 - 12.8, respectively. The mean HAQ-DI score was lower in the APR 20mg group at 1.125 compared with 1.25 in both the PBO and APR 30mg treatment groups. The mean PtGA and PhGA were similar in the 3 treatment groups at 55.3 - 58.8 mm and 54.1 - 55.7 mm, respectively. The mean baseline CRP readings were similar in the APR treatment groups (0.844 - 0.904 mg/dL) but slightly higher in the PBO arm at 1.066

mg/dL. Across the treatment groups, 62.5% (315/504) had active enthesitis with a mean (median) baseline MASES score of 5.0 (4.0). Dactylitis at baseline was recorded in 39.3% (198/504) with a mean (median) baseline dactylitis severity score of 3.3 (2.0).

The majority of subjects (97.6%; 492/504) had received prior treatment with conventional and/or biologic DMARDs, with almost half (47.8%; 241/504) having been previously treated with only 1 conventional DMARD, and approximately one quarter (23.6%; 119/504) having previously received biologic DMARD, the most common of which were anti-TNF drugs (21.6%; 109/504). Almost half of the anti-TNF experienced subjects (9.3%; 47/504) recorded a prior lack of sufficient response to this therapy (either loss of response, partial response or no response). A small proportion of subjects (6.0%; 30/504) had experienced 2 or more anti-TNF therapies. Regarding prior conventional DMARD exposure, 83.5% (421/504) had a history of MTX use, 27.2% (137/504) had previously tried SSZ and 14.1% (71/504) had a history of LEF therapy.

Subjects were stratified to study treatment by baseline DMARD use. A total of 54.2% (273/504) of subjects (evenly distributed among the 3 treatment groups) were taking MTX at baseline at a median dose of 15 mg/week (mean of 16.63 mg/week), and 10.7% (54/504) were taking SSZ and 6.0% (30/504) were taking LEF. The majority of patients (71.6%; 361/504) were taking NSAIDs at baseline as well. A higher percentage of patients (14.9%; 25/168) in the APR 20mg group compared with the other 2 treatment groups (7.1% [12/168] in the PBO arm and 9.5% [16/168] in the APR 30mg group). In all 3 groups, the baseline median oral CS dose was 5.0 mg/day. In addition, 15-19% of patients were taking narcotic analgesics at enrolment.

The incidence of relevant co-morbid conditions was similar in the treatment groups. A past history of hypertension was recorded in 39.5% of all subjects (199/504), 19.0% (96/504) reported hyperlipidaemia and 7.3% (37/504) had type 2 diabetes mellitus. Past history of depression was recorded in 16.9% of patients (85/504). Twelve subjects had potential tuberculosis (TB) risk, including latent TB (7 subjects), past pulmonary TB (3 subjects) and positive tuberculin skin test (2 subjects). Almost half of all subjects (45.8%; 231/504) were current alcohol drinkers and 18.3% (92/504) were current tobacco users.

7.1.1.1.11.2. Study PSA-003

Overall, subjects had a mean age of 50.9 years (range: 19 - 80 years), over half (56.8%; 275/484) were female, and most (95.0%; 460/484) were of Caucasian ethnicity. The mean BMI was 29.32 kg/m2, and the majority of subjects (59.1%; 286/484) had a BMI < 30 kg/m2. In terms of geographical regions, patients were recruited from Europe (64.0%; 310/484) followed by North America (24.0%; 116/484) and ROW countries (12.0%; 58/484), which included Russia, China, Taiwan and South Africa. The treatment groups were well balanced with respect to baseline demographic characteristics.

The treatment groups were also similar with respect to baseline PsA features. The mean duration of PsA for all subjects was 7.47 years (median 4.75 years, range: 0.1 - 54.4 years). The predominant subtypes of PsA were symmetrical polyarthritis (64.3%; 311/484) followed by asymmetrical oligoarthritis (27.7%; 134/484). Nearly all subjects (99.0%; 479/484) had a confirmed diagnosis of PSOR with a median duration of 13.9 years. The mean PASI score was 7.88 (median 5.20), and 47.7% (231/484) of subjects had at least 3% BSA involvement at baseline.

In terms of PsA disease activity at baseline, the PBO group had slightly lower mean numbers of tender and swollen joints at 18.0 and 9.2 (respectively) compared with the APR groups (20.3 - 21.0 and 10.3 - 10.4, respectively). The mean HAQ-DI scores were similar: 1.164 in the PBO group, 1.133 in the APR 20mg arm and 1.220 in the APR 30mg group. The mean PtGA and PhGA were similar in the 3 treatment groups at 56.3 mm and 54.8 mm, respectively. The mean baseline CRP readings were similar in the APR 20mg and PBO treatment groups (1.02 - 1.08 mg/dL) but lower in the APR 30mg arm at 0.88 mg/dL. Across the treatment groups, 64.5%

(312/484) had active enthesitis with a mean (median) baseline MASES score of 4.5 (4.0). Dactylitis was recorded in 44.6% (216/484) had pre-existing dactylitis with a mean (median) baseline dactylitis severity score of 2.6 (2.0).

The majority of subjects (98.8%; 478/484) had received prior treatment with conventional and/or biologic DMARDs, with almost half (47.1%; 228/484) having been previously treated with only 1 conventional DMARD, and 15.3% (74/484) having previously received biologic DMARD, the most common of which were anti-TNF drugs (14.3%; 69/484). Less than half of the anti-TNF experienced subjects (5.2%; 25/484) recorded a prior lack of sufficient response to this therapy (either loss of response, partial response or no response) with AEs/tolerability issues being a similar reason for discontinuation (4.5%; 22/484). A small proportion of subjects (5.6%; 27/484) had experienced 2 or more anti-TNF therapies. Regarding prior conventional DMARD exposure, 86.0% (416/484) had a history of MTX use, 35.3% (171/484) had previously tried LEF and 20.5% (99/484) had a history of SSZ therapy.

Subjects were stratified to study treatment by baseline DMARD use. A total of 57.6% (279/484) of subjects (evenly distributed among the 3 treatment groups) were taking MTX at baseline at a median dose of 15 mg/week (mean of 14.89 mg/week), and 9.7% (47/484) were taking SSZ and 11.4% (55/484) were taking LEF. At baseline, 61.0% (295/484) of subjects were receiving 1 conventional DMARD, 9.1% (44/484) were taking 2 DMARDs concurrently and only 1 subject (0.2%) was taking 3 DMARDs. The majority of patients (69.6%; 337/484) were taking NSAIDs at baseline as well. A higher percentage of patients (22.1%; 36/163) in the APR 20mg group compared with the other 2 treatment groups (12.6% [20/159] in the PBO arm and 15.4% [25/162] in the APR 30mg group). In all 3 groups, the baseline median oral CS dose was 5.0 mg/day. In addition, approximately 14% of patients in each group were taking narcotic analgesics.

The incidence of relevant co-morbid conditions was similar in the treatment groups. A past history of hypertension was recorded in 41.5% of all subjects (201/484), 14.5% (70/484) reported hyperlipidaemia and 7.4% (36/484) had type 2 diabetes mellitus. Past history of depression was recorded in 13.2% of patients (64/484). Eight subjects had a risk of developing TB, including latent TB (3 subjects), past pulmonary TB (2 subjects) and positive tuberculin skin test (3 subjects). Just over half of all subjects (51.4%; 249/484) were current alcohol drinkers and 21.1% (102/484) were current tobacco users.

7.1.1.1.11.3. Study PSA-004

The majority of subjects enrolled in this trial were Caucasian (95.4%; 482/505) and just over half (53.3%; 269/505) were female. Overall, patients had a mean age of 49.7 years (range: 18 - 77 years), and 9.1% (46/505) of all subjects were aged 65 years or older. The mean BMI of the enrolled cohort was 29.6 kg/m^2. By geographic region, subjects came from Europe (45.9%; 232/505), North America (32.5%; 164/505) and ROW countries (21.6%; 109/505) including Australia, South Korea and Russia. The 3 treatment groups were well matched for demographic characteristics.

The treatment groups were also similar with respect to baseline PsA features. The mean duration of PsA for all subjects was 7.33 years (median 5.10 years, range: 0.2 - 57.3 years). The predominant subtypes of PsA were symmetrical polyarthritis (58.4%; 295/505) followed by asymmetrical oligoarthritis (26.9%; 136/505). All subjects had a confirmed diagnosis of PSOR with a median duration of 15.3 years. The mean PASI score at baseline was 7.69 (median 5.50), and more than half of subjects (55.2%; 279/505) had at least 3% BSA involvement at baseline.

In terms of PsA disease activity at baseline, the mean numbers of tender and swollen joints were similar for all 3 treatment groups at 18.3-20.9 and 11.1 - 11.6, respectively. The mean HAQ-DI score was slightly lower in the APR 20mg group at 1.12 compared with 1.17 in the PBO and 1.18 in the APR 30mg treatment group. The mean PtGA and PhGA were similar in the 3 treatment groups at 52.8 - 56.1 mm and 55.0 - 56.8 mm, respectively. The mean baseline CRP readings

were similar in the APR 20mg and PBO groups (0.967 - 0.996 mg/dL) but slightly higher in the APR 30mg arm at 1.148 mg/dL. Across the treatment groups, 63.0% (318/505) had active enthesitis with a mean (median) baseline MASES score of 4.4 (3.0). Dactylitis at baseline was recorded in 44.0% (222/505) with a mean (median) baseline dactylitis severity score of 3.8 (2.0).

All but 1 subject had received prior treatment with conventional and/or biologic DMARDs, with half (50.3%; 254/505) having been previously treated with only 1 conventional DMARD, and 27.9% (141/505) having previously received biologic DMARD, the most common of which were anti-TNF drugs (26.1%; 132/505). About one third of the anti-TNF experienced subjects (9.3%; 47/505) recorded a prior lack of sufficient response to this therapy (either loss of response, partial response or no response) with loss of drug access being the most common reason for discontinuation (14.7%; 74/505). A small proportion of subjects (6.3%; 32/505) had experienced 2 or more anti-TNF therapies. Regarding prior conventional DMARD exposure, 85.5% (432/505) had a history of MTX use, 22.8% (115/505) had previously tried SSZ and 13.3% (67/505) had a history of LEF use.

Subjects were stratified to study treatment by baseline DMARD use. A total of 51.9% (262/505) of subjects (evenly distributed among the 3 treatment groups) were taking MTX at baseline at a median dose of 15 mg/week (mean of 14.75 mg/week), and 6.7% (34/505) were taking SSZ and 5.0% (25/505) were taking LEF. At baseline, 57.4% (290/505) of subjects were receiving 1 conventional DMARD and 3.2% (16/505) were taking 2 DMARDs concurrently. The majority of patients (70.7%; 357/505) were taking NSAIDs at baseline as well. A higher percentage of patients (20.1%; 34/169) in the APR 20mg group compared with the other 2 treatment groups (9.5% [16/169] in the PBO arm and 13.8% [23/167] in the APR 30mg group). In all 3 groups, the baseline median oral CS dose was 5.0 mg/day. In addition, 12.3% (62/505) of patients in each group were taking narcotic analgesics.

The incidence of relevant co-morbid conditions was similar in the treatment groups. A past history of hypertension was recorded in 39.4% of all subjects (199/505), 11.7% (59/505) reported hyperlipidaemia and 7.3% (37/505) had type 2 diabetes mellitus. Past history of depression was recorded in 13.5% of patients (68/505). Twelve subjects had a risk of developing TB, including latent TB (2 subjects), past TB infection (3 subjects) and positive tuberculin skin test (7 subjects).

7.1.1.1.11.4. Study PSA-005

Overall, subjects had a mean age of 49.4 years (range: 18 - 77 years), just over half (52.6%; 277/527) were female, and nearly all (98.7%; 520/527) were of Caucasian ethnicity. The mean BMI was 29.4 kg/m2, and the majority of subjects (60.2%; 317/527) had a BMI < 30 kg/m2. In terms of geographical regions, patients were recruited from Europe (45.2%; 238/527), North America (29.4%; 155/527) and ROW countries (25.4%; 134/527), which included Australia, New Zealand and Russia. In general, the treatment groups were well balanced with respect to demographic characteristics although patients in both of the APR treatment groups were more likely to be female (54.4%) versus those in the PBO arm (48.9%).

The treatment groups were similar with respect to baseline PsA features. The mean duration of PsA for all subjects was 3.4 years (median 1.1 years, range: 0.0 - 31.4 years). The predominant subtypes of PsA were symmetrical polyarthritis (63.1%; 323/527) followed by asymmetrical oligoarthritis (30.0%; 158/527). All subjects had a confirmed diagnosis of PSOR with a median duration of 11.9 years. The mean PASI score was 7.2 (median 5.05), and 58.1% (306/527) of subjects had at least 3% BSA involvement at baseline.

In terms of PsA disease activity at baseline, the mean numbers of tender and swollen joints were similar for all 3 treatment groups at 20.1 and 11.2, respectively. The mean HAQ-DI score was slightly lower in the PBO group at 1.01 compared with 1.07 - 1.13 in the APR treatment groups. The mean PtGA and PhGA were similar in the 3 treatment groups at 53.3 mm and 53.4 mm,

respectively. The mean baseline CRP readings were similar in the APR treatment groups (0.8-0.9 mg/dL) but higher in the PBO arm at 1.1 mg/dL. Across the treatment groups, 64.9% (343/527) had active enthesitis with a mean (median) baseline MASES score of 3.8 (3.0). Approximately half of all subjects (49.9%; 263/527) had pre-existing dactylitis with a mean (median) baseline dactylitis severity score of 3.3 (2.0).

Overall, 76.7% (404/527) of subjects were taking concomitant PsA related therapies (non-DMARD) at baseline at a comparable frequency between the treatment groups. Most subjects (73.1%; 385/527) were using NSAIDs, with a small percentage of patients (7.2%; 38/527) taking oral CS at a mean (median) daily dose of 6.7mg (5.0mg). In addition, a small percentage of patients (6.6%; 35/527) were taking narcotic analgesics.

7.1.1.1.12. Results for the primary efficacy outcome

7.1.1.1.12.1. Study PSA-002

All 3 of the Phase III studies whereby background concomitant DMARD therapy could be continued demonstrated a statistically significant treatment effect with APR (both dose regimens) compared with PBO (Table 9). In the 3 PsA studies, the average adjusted treatment effect sizes for the APR 20mg and APR 30mg twice-daily regimens were 13% and 18%, respectively, indicating an apparent dose effect with APR, but this observation was not statistically significant (p = 0.14 for APR 30mg twice daily versus APR 20mg twice daily).

Table 9: Proportion of Subjects Achieving Modified ACR20 Response at 16 Weeks in Studies PSA-002, PSA-003 and PSA-004

	Placebo	APR 20 BID			APR 30 BID		
Study	n/N (%)[a]	n/N (%)[a]	Trt. Effect[b]	P-value[c]	n/N (%)[a]	Trt. Effect[b]	P-value[c]
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 determination of response 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.

[b] Treatment effect is the adjusted difference in proportions, calculated as the weighted average of the treatment differences across the strata of baseline disease-modifying antirheumatic drug (DMARD) use and (for Study PSA-004 only) baseline body surface area (BSA) with psoriasis, with the Cochran-Mantel-Haenszel weights.

[c] 2-sided P-value is based on Cochran-Mantel-Haenszel test adjusting for baseline DMARD use and (for Study PSA-004 only) baseline BSA with psoriasis. P-values in bold are considered statistically significant.

In Study PSA-002, statistically significant greater proportions of subjects in the APR 20mg twice daily and APR 30mg twice daily treatment groups achieved a modified ACR20 response at week 16 (30.4% [51/168] and 38.1% [64/168], respectively) compared with PBO (19% [32/168]; p = 0.0166 and p = 0.0001, respectively). The observed positive treatment effect with APR was consistently seen in the multiple sensitivity analyses that included different analysis populations (FAS and PP) and various assumptions for missing data (e.g. NRI and LOCF methods).

7.1.1.1.12.2. Study PSA-003

In Study PSA-003, statistically significant greater proportions of subjects in the APR 20mg and APR 30mg treatment groups achieved a modified ACR20 response at week 16 (37.4% [61/163] and 32.1% [52/162], respectively) compared with PBO (18.9% [30/159]; p = 0.0002 and p = 0.0060, respectively). No difference in response to APR according to dose regimen was observed in this trial (p = 0.31). Various sensitivity analyses confirmed the robustness of the primary analysis findings.

7.1.1.1.12.3. Study PSA-004

A statistically greater proportion of subjects in the APR 20mg and APR 30mg treatment groups achieved a modified ACR20 response at week 16 (28.4% [48/169] and 40.7% [68/167], respectively) compared with PBO (18.3% [31/169]; p = 0.0295 and p< 0.0001, respectively). In this trial, a statistically greater rate of response was seen with APR 30mg twice daily versus APR 20mg twice daily (p = 0.02). Sensitivity analyses supported the primary efficacy analysis results.

7.1.1.1.12.4. Study PSA-005

In Study PSA-005, a statistically significant greater proportion of subjects in the APR 20mg and APR 30mg treatment groups achieved a modified ACR20 response at week 16 (28.0% [49/175] and 30.7% [54/176], respectively) compared with PBO (15.9% [28/176]; p = 0.0062 and p = 0.0010, respectively). No difference in response to APR according to dose regimen was observed in this trial. The observed positive treatment effect with APR was consistently seen in the multiple sensitivity analyses that included different analysis populations (FAS and PP) and various assumptions for missing data (e.g. NRI and LOCF methods applied to missing ACR component data).

In the subgroup analyses of the modified ACR20 response at week 16, APR consistently demonstrated a treatment effect over PBO across multiple demographic and disease characteristics, with 1 exception. Subjects with a weight > 100 kg (or BMI > 40 kg/m2) had no greater rate of response to APR than PBO. In patients weighing > 100 kg treated with APR 30mg twice daily the rate of ACR20 response was 30.2% (13/43) versus 25.0% (7/38) in the PBO group (treatment difference of 5.2; 95% CI -15.9, 28.3). In the APR 20mg twice daily group the rate of response was 25.8% (8/31) in those weighing > 100 kg (treatment difference versus PBO of 0.8; 95% CI -21.4, 23.0).

7.1.1.1.13. Results for other efficacy outcomes

7.1.1.1.13.1. Study PSA-002

For the key secondary efficacy endpoint, subjects in the APR 20mg and APR 30mg twice-daily treatment groups had statistically significant greater mean improvements (reductions) in the HAQ-DI score compared with PBO. The LS mean changes from baseline in the HAQ-DI score at week 16 for the APR 20mg and APR 30mg treatment groups were -0.198 and -0.244, respectively, versus -0.086 in the PBO group (p = 0.0252 and p = 0.0017, respectively) (Table 10). These improvements were maintained at week 24 in both APR treatment groups (-0.211 and -0.258, respectively, versus -0.076; p= 0.0091 and 0.0005, respectively). A dose effect with APR was again observed.

Table 10: Changes from Baseline in HAQ-DI Score at 16 Weeks in Studies PSA-002, PSA-003 and PSA-004

	Placebo			APR 20 BID					APR 30 BID				
Study	n[a]	Mean Baseline Value	LS Mean Change (SE)	n[a]	Mean Baseline Value	LS Mean Change (SE)	LS Mean Difference	P-value[b]	n[a]	Mean Baseline Value	LS Mean Change (SE)	LS Mean Difference	P-value[b]
PSA-002	165	1.206	-0.086 (0.0360)	163	1.141	-0.198 (0.0364)	-0.113	**0.0252**	159	1.231	-0.244 (0.0364)	-0.159	**0.0017**
PSA-003	153	1.147	-0.053 (0.0358)	159	1.128	-0.157 (0.0351)	-0.104	**0.0320**	154	1.222	-0.193 (0.0354)	-0.140	**0.0042**
PSA-004	163	1.160	-0.065 (0.0335)	163	1.134	-0.131 (0.0337)	-0.066	0.1619	160	1.160	-0.192 (0.0339)	-0.127	**0.0073**

APR = apremilast; BID = twice daily; FAS = full analysis set; LOCF = last observation carried forward; LS = least-squares; SE = standard error.
[a] For subjects who discontinued from the study prior to Week 16, the last available postbaseline value observed prior to discontinuation was carried forward to Week 16
[b] P-value based on an analysis of covariance model for the change from baseline at the respective time point, with treatment group, baseline disease-modifying antirheumatic drug (DMARD) use, and (for Study PSA-004 only) involvement of ≥ 3% body surface area with psoriasis at Baseline as factors, and the baseline value as a covariate. P-values in bold are considered statistically significant.

The improvement in the rate of modified ACR20 response with APR therapy versus PBO at week 16 was maintained at week 24. A statistically significantly greater percentage of subjects treated with APR achieved a modified ACR20 response compared with PBO (25.6% [43/168] for APR 20mg and 35.1% [59/168] versus 13.1% [22/168] for PBO; p = 0.0038 and p < 0.0001, respectively). There was an apparent dose effect with APR observed.

A greater proportion of subjects in both APR groups achieved ACR50 response at week 16 and 24 compared with PBO (nominal p < 0.005) (Table 11). Moreover, a higher percentage of subjects treated with APR 20mg twice daily reached ACR70 response at week 16 and 24 compared to PBO (nominal p < 0.02). However, the APR 30mg dose arm also demonstrated a statistically greater ACR70 response at week 24 (9.5% versus 0.6%; p = 0.0001), but not at week 16 versus PBO (3.1% versus 1.2%; p = 0.0792).

Table 11: Proportion of Subjects Achieving Modified ACR20/50/70 Response at Weeks 16 and 24 in Studies PSA-002, PSA-003 and PSA-004

Visit Study	Placebo n/N (%)[a]	APR 20 BID n/N (%)[a]	Trt. Effect[b]	P-value[c]	APR 30 BID n/N (%)[a]	Trt. Effect[b]	P-value[c]
Modified ACR 20 Response							
Week 16 (Primary Endpoint)							
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**
Week 24							
PSA-002	22/168 (13.1)	43/168 (25.6)	12.4	**0.0038**	59/168 (35.1)	22.2	**< 0.0001**
PSA-003	25/159 (15.7)	51/163 (31.3)	15.7	**0.0009**	40/162 (24.7)	9.2	**0.0394**
PSA-004	26/169 (15.4)	45/169 (26.6)	11.1	*0.0110*	52/167 (31.1)	15.5	**0.0007**
Modified ACR 50 Response							
Week 16							
PSA-002	10/168 (6.0)	26/168 (15.5)	9.5	*0.0049*	27/168 (16.1)	10.3	*0.0027*
PSA-003	8/159 (5.0)	24/163 (14.7)	9.8	*0.0034*	17/162 (10.5)	5.6	0.0589
PSA-004	14/169 (8.3)	21/169 (12.4)	4.2	0.2052	25/167 (15.0)	6.8	0.0520
Week 24							
PSA-002	7/168 (4.2)	24/168 (14.3)	10.1	*0.0014*	32/168 (19.0)	14.9	*< 0.0001*
PSA-003	14/159 (8.8)	23/163 (14.1)	5.4	0.1323	19/162 (11.7)	3.1	0.3629
PSA-004	13/169 (7.7)	23/169 (13.6)	5.8	0.0807	27/167 (16.2)	8.3	*0.0180*
Modified ACR 70 Response							
Week 16							
PSA-002	2/168 (1.2)	10/168 (6.0)	4.8	*0.0192*	7/168 (4.2)	3.1	0.0792
PSA-003	1/159 (0.6)	6/163 (3.7)	3.1	0.0570	2/162 (1.2)	0.6	0.5620
PSA-004	4/169 (2.4)	8/169 (4.7)	2.3	0.2527	6/167 (3.6)	1.2	0.5154
Week 24							
PSA-002	1/168 (0.6)	9/168 (5.4)	4.7	*0.0104*	17/168 (10.1)	9.5	*0.0001*
PSA-003	5/159 (3.1)	9163 (5.5)	2.4	0.2929	4/162 (2.5)	-0.6	0.7273
PSA-004	6/169 (3.6)	7/169 (4.1)	0.6	0.7870	9/167 (5.4)	1.8	0.4230

ACR 20/50/70 = American College of Rheumatology 20%/50%/70% response; APR = apremilast; BID = twice daily; FAS = full analysis set; NRI = nonresponder imputation; Trt. = treatment

[a] Subjects who discontinued early prior to the respective visits, subjects who escaped early at Week 16 (for the Week 24 analyses), and subjects who did not have sufficient data for a definitive determination of response status at the respective visits 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 the respective visits. There was no imputation for other missing ACR component scores.

[b] Treatment effect is the adjusted difference in proportions, calculated as the weighted average of the treatment differences across the strata of baseline disease-modifying antirheumatic drug (DMARD) use and (for Study PSA-004 only) baseline body surface area (BSA) with psoriasis, with the Cochran-Mantel-Haenszel (CMH) weights.

[c] 2-sided P-value is based on CMH test adjusting for baseline DMARD use and (for Study PSA-004 only) baseline BSA with psoriasis. P-values in bold are considered statistically significant. P-values in italics are ≤ 0.050 and considered nominally significant, as hierarchical testing was stopped after secondary endpoint #4 for both apremilast groups in Study PSA-002; after secondary endpoint #2 for the APR 20 BID treatment group and #5 for the APR 30 BID treatment group in Study PSA-003; and after the primary endpoint for the APR 20 BID treatment group and secondary endpoint #7 for the APR 30 BID treatment group in Study PSA-004.

At week 16, a statistically greater proportion of subjects in the APR 30mg group achieved a modified PsARC response (46.4%; 78/164) compared with PBO (29.8% [50/168]; p = 0.0017), which was maintained at week 24 (42.9% [72/168] versus 18.5% [31/168]; p < 0.0001). The

proportion of subjects in the APR 20mg arm achieving a modified PsARC response at week 24 was significantly greater than PBO (31.0% [52/168] versus 18.5% [31/168]; p = 0.0079), however, the comparison at week 16 was not statistically significant (38.7% [65/168] versus 29.8% [50/168]; p = 0.0862). A dose-response effect with APR was observed for the rate of PsARC response at weeks 16 and 24. At week 16, the proportion of subjects with a DAS 28 (CRP) score ≥ 3.2 in the APR treatment groups had decreased from 92 - 94% to approximately 74 - 76% while the proportion with a DAS 28 (CRP) score < 3.2 (indicating low disease activity) had increased from 6 - 7% to 24 - 26% (including 13.1% of subjects in both APR treatment groups having a DAS28 (CRP) score < 2.6 (i.e. remission). At week 24, the proportion of subjects with a DAS 28 (CRP) score < 2.6 was maintained in the APR 20mg group (12.5%; 21/168) and increased in the APR 30mg arm (19.0%; 32/168). By comparison, the distribution of DAS 28 (CRP) score did not appreciably change over time from baseline in the PBO-treated subjects. At baseline, all but 1 subject in the APR 20mg group had a CDAI score > 22. Therapy with APR had a positive effect on CDAI scores as indicated by the proportion of subjects with high disease activity at baseline which decreased by week 16, and the percentage of subjects with disease remission or low disease activity at week 16 compared to baseline. Specifically, the proportion of subjects with high disease activity decreased from baseline to week 16 - 61.3% (103/168) to 36.3% (61/168) for APR 20mg subjects and 70.8% (119/168) to 35.7% (60/168) for APR 30mg patients. The proportion of subjects with low disease activity increased from baseline to week 16 - 3.0% (5/168) to 18.5% (31/168) for APR 20mg subjects and 3.6% (6/168) to 21.4% (36/168) for APR 30 mg patients. These effects were maintained at week 24.

Among subject with enthesitis at baseline, APR treatment (both doses) produced a numerically greater LS mean reduction (improvement) in the MASES score at week 16 and 24 compared to PBO, however, only the comparison between APR 30mg and PBO at week 24 was statistically significant. For the PBO group, the LS mean reduction in MASES score at week 16 was -0.9, and at week 24 was -0.8 (baseline mean score 5.4). For the APR 20mg arm, the LS mean reduction in MASES score at week 16 was -1.4, and at week 24 was -1.6 (baseline mean score 5.0). For the APR 30mg group, the LS mean reduction in MASES score at week 16 was -1.3, and at week 24 was -1.6 (baseline mean score 4.4). Among subjects with pre-existing dactylitis, APR treatment (both doses) produced a numerically greater LS mean reduction (improvement) in the dactylitis score at week 16 and 24 compared to PBO, but none of the comparisons between APR and PBO were statistically significant. For the PBO group, the LS mean reduction in the dactylitis score at week 16 was -1.4, and at week 24 was -1.3 (baseline mean score 3.3). For the APR 20mg arm, the LS mean reduction in the dactylitis score at week 16 was -1.9, and at week 24 was -2.0 (baseline mean score 3.9). For the APR 30mg group, the LS mean reduction in the dactylitis score at week 16 was -1.7, and at week 24 was -1.8 (baseline mean score 2.9).

Subjects treated with APR achieved statistically significant (p < 0.05) LS mean improvements (increases) from baseline in the SF-36 Physical Functioning (PF) domain score at week 16 compared with PBO. The improvements were dose-dependent and maintained at week 24. The LS mean improvement in the APR 20mg group was 3.5 points at both week 16 and 24 (baseline mean of 38.7). For the APR 30mg treatment group, the LS mean improvements were 4.2 points at 16 weeks and 5.0 points at 24 weeks (baseline mean of 38.5). In the control arm, the LS mean improvement at week 16 was 1.8 points, and 1.45 points at week 24 (baseline mean of 35.9). Subjects in the APR 30mg treatment group recorded a statistically greater (p = 0.0165) mean improvement (increase from baseline) in the FACIT-F score at week 16 compared with PBO, which was maintained at week 24 (p = 0.022). The LS mean improvement observed in the APR 30mg group at week 16 was 3.88 points, and at week 24 was 3.33 points (baseline mean score 30.0). No differences in FACIT-F scores were observed between the APR 20mg treatment group (1.68 points at week 16 and 1.52 points at week 24; baseline mean 32.1) and PBO at week 16 or 24 (1.55 points at week 16 and 1.12 points at week 24; baseline mean 29.3).

APR demonstrated maintenance of benefit across all measures of efficacy at 52 weeks of treatment. Sustained improvement in signs and symptoms of PsA, as measured by the modified

ACR20 response, continued up to week 52. Analysed using observed data, the modified ACR20 response rates recorded for the APR 20mg and APR 30mg treatment groups at week 52 were 63.0% (75/119) and 54.6% (71/130), respectively, for subjects who remained in the trial. Improved physical functioning, as measured by the LS mean change from baseline in the HAQ-DI score also continued up to week 52. The improvements in the HAQ-DI score observed in the APR 20mg and APR 30mg treatment groups at week 52 were -0.369 and -0.318, respectively, in subjects remaining in the study. Across all other endpoints, including those assessing disease activity, physical functioning, enthesitis and dactylitis, sustained improvements were observed up to week 52 in subjects remaining in the study.

7.1.1.1.13.2. Study PSA-003

The LS mean changes from baseline in the HAQ-DI score at week 16 were also statistically greater in the APR treatment groups (-0.157 for the 20mg group and -0.193 for the 30mg arm) versus -0.053 in the PBO group ($p = 0.0320$ and $p = 0.0042$, respectively). These LS mean improvements were maintained at week 24 in both APR treatment groups, but only the improvement in the APR 30mg twice daily treatment group remained statistically significant compared with PBO (-0.165 in the APR 20mg group and -0.206 in the APR 30mg arm versus -0.085 in the PBO group; $p = 0.1179$ and 0.0191, respectively).

At week 24, a statistically greater proportion of patients treated with APR (31.3% [51/163] in the 20mg group and 24.7% [40/162] in the 30mg arm) achieved a modified ACR20 response compared with PBO (15.7% [25/159]; $p = 0.0009$ and $p = 0.0394$, respectively). In Study PSA-003, a greater proportion of subjects in both APR groups achieved ACR50 response at week 16 and 24 compared with PBO, but none of these pair-wise comparisons reached statistical significance except for APR 20mg versus PBO at 16 weeks. Moreover, a slightly higher percentage of subjects treated with APR (either dose) reached ACR70 response at week 16 and 24 compared to PBO, but none of these pair-wise comparisons were statistically significant.

At week 16, a statistically greater proportion of subjects treated with APR achieved a modified PsARC response (47.9% [78/163] in the 20mg group and 48.1% [78/162] in the 30mg arm) compared with PBO (33.3% [53/159]; $p < 0.0071$), which was maintained at week 24 for APR 20mg group versus PBO (33.9% [65/163] versus 24.5% [39/159]; $p = 0.0026$). The proportion of subjects in the APR 30mg arm achieving a modified PsARC response at week 24 was numerically higher than PBO (32.1% [52/162] versus 24.5% [39/159]), however, this comparison was not statistically significant ($p = 0.1195$). At week 16, the proportion of subjects with a DAS 28 (CRP) score ≥ 3.2 in the APR treatment groups had decreased from 89 - 94% to approximately 65 - 67% while the proportion with a DAS 28 (CRP) score < 3.2 (indicating low disease activity) had increased from 6 - 10% to 26 - 30% (including 30.1% [49/163] of subjects in the APR 20mg treatment group and 26.7% [43/162] in the APR 30mg arm having a DAS28 (CRP) score < 2.6 (i.e. remission). At week 24, the proportion of subjects with a DAS 28 (CRP) score < 2.6 was maintained in both APR treatment groups (16.6% [27/163] in the 20mg group and 14.8% [24/162] in the 30mg arm). By comparison, the distribution of DAS 28 (CRP) score did not appreciably change over time from baseline in the PBO-treated subjects. At baseline, more than 50% of subjects in each of the 3 treatment groups had a CDAI score > 22. Therapy with APR had a positive effect on CDAI scores as indicated by the proportion of subjects with high disease activity at baseline which decreased by week 16, and the percentage of subjects with disease remission or low disease activity at week 16 compared to baseline. The proportion of subjects with high disease activity at baseline which decreased by week 16 was 56.4% (92/163) to 28.2% (46/163) for APR 20mg subjects and 54.9% (89/162) to 29.6% (48/162) for APR 30mg patients. The proportion of subjects with low disease activity increased from baseline to week 16 – 4.3% (7/163) to 24.5% (40/163) for APR 20mg subjects and 2.5% (4/162) to 24.7% (40/162) for APR 30 mg patients. These effects were maintained at week 24.

Among subject with enthesitis at baseline, APR treatment (both doses) produced numerically similar LS mean reduction (improvement) in the MASES score at week 16 and 24 compared to

PBO, and none of the treatment comparisons between APR and PBO were statistically significant. For the PBO group, the LS mean reduction in MASES score at week 16 was -1.0, and at week 24 was -0.9 (baseline mean score 4.7). For the APR 20mg arm, the LS mean reduction in MASES score at week 16 was -0.9, and at week 24 was -0.9 (baseline mean score 4.4). For the APR 30mg group, the LS mean reduction in MASES score at week 16 was -1.4, and at week 24 was -1.3 (baseline mean score 4.4). Similarly, among subjects with pre-existing dactylitis, APR treatment (both doses) produced numerically similar LS mean reduction (improvement) in the dactylitis score at week 16 and 24 compared to PBO, and none of the comparisons between APR and PBO were statistically significant. For the PBO group, the LS mean reduction in the dactylitis score at week 16 was -1.1, and at week 24 was -1.1 (baseline mean score 2.7). For the APR 20mg arm, the LS mean reduction in the dactylitis score at week 16 was -0.8, and at week 24 was -0.9 (baseline mean score 2.8). For the APR 30mg group, the LS mean reduction in the dactylitis score at week 16 was -1.3, and at week 24 was -1.4 (baseline mean score 2.6).

Subjects treated in the APR 30mg twice daily group achieved statistically significant ($p < 0.05$) LS mean improvements (increases) from baseline in the SF-36 Physical Functioning (PF) domain score at week 16 compared with PBO. This improvement was maintained at week 24. The LS mean improvement in the APR 30mg group was 2.9 and 3.3 points at week 16 and 24, respectively (baseline mean of 37.7). For the APR 20mg treatment group, the LS mean improvements were 2.2 points at 16 weeks and 3.0 points at 24 weeks (baseline mean of 34.6). In the control arm, the LS mean improvement at week 16 was 0.8 points, and 1.4 points at week 24 (baseline mean of 35.9). Subjects in the APR 30mg treatment group recorded a statistically greater ($p < 0.032$) mean improvement (increase from baseline) in the FACIT-F score at week 16 and 24 compared with PBO. The LS mean improvement observed in the APR 30mg group at week 16 was 2.75 points, and at week 24 was 2.65 points (baseline mean score 29.9). No differences in FACIT-F scores were observed between the APR 20mg treatment group (0.9 points at week 16 and 0.7 points at week 24; baseline mean 30.7) and PBO at week 16 or 24 (0.6 points at week 16 and 0.5 points at week 24; baseline mean 31.8).

At week 52, APR demonstrated maintenance of effect across all measures of efficacy in those subjects who continued to receive up to 52 weeks of treatment. At week 52 (using observed data), the modified ACR20 response rates recorded for the APR 20mg group was 52.9% (64/121) and for the APR 30mg arm was 52.6% (61/116). The LS mean change from baseline in the HAQ-DI scores were -0.192 in the APR 20mg group and -0.330 in the APR 30mg cohort (for subjects remaining in the study).

7.1.1.1.13.3. Study PSA-004

For the key secondary endpoint of LS mean change from baseline to week 16 in the HAQ-DI score, only the APR 30mg treatment group (-0.192) had statistically significant greater improvement (reduction) compared with PBO (-0.065; $p = 0.0073$). This improvement was maintained at week 24 (-0.192 versus -0.053, respectively; $p = 0.0050$). However, no statistically significant improvement in the LS mean change in the HAQ-DI score for the APR 20mg treatment group compared with PBO was observed at either week 16 or 24 (-0.131 and -0.137, respectively).

At week 24, a statistically greater percentage of patients treated with APR 30mg twice daily achieved a modified ACR20 response (31.1%; 52/167) compared with PBO (15.4% [26/169]; $p = 0.0007$). However, although the rate of ACR20 response was numerically higher in the APR 20mg twice daily arm (26.6%; 45/169), this did not reach statistical significance when compared to PBO ($p = 0.0110$).

In Study PSA-004, a greater proportion of subjects in both APR groups achieved ACR50 response at week 16 and 24 compared with PBO, but none of these pair-wise comparisons reached statistical significance except for APR 30mg versus PBO at 24 weeks. Moreover, a slightly higher percentage of subjects treated with APR (either dose) reached ACR70 response

at week 16 and 24 compared to PBO, but none of these pair-wise comparisons were statistically significant.

At week 16, a statistically greater proportion of subjects in the APR 30mg group achieved a modified PsARC response (52.7%; 88/167) compared with PBO (27.2% [46/169]; $p < 0.0001$), which was maintained at week 24 (44.3% [74/167] versus 23.1% [39/169]; $p < 0.0001$). The proportion of subjects in the APR 20mg arm achieving a modified PsARC response at week 16 was significantly greater than PBO (37.9% [64/169] versus 27.2% [46/169]; $p = 0.0372$), however, the comparison at week 24 was not statistically significant (32.0% [54/169] versus 23.1% [39/169]; $p = 0.0661$). A dose-response effect with APR was observed for the rate of PsARC response at weeks 16 and 24. At week 16, the proportion of subjects with a DAS 28 (CRP) score ≥ 3.2 in the APR treatment groups had decreased from 89-94% to approximately 69 - 71% while the proportion with a DAS 28 (CRP) score < 3.2 (indicating low disease activity) had increased from 6 - 10% to 29 - 30% (including 18% of subjects in both APR treatment groups having a DAS28 (CRP) score < 2.6 (i.e. remission). At week 24, the proportion of subjects with a DAS 28 (CRP) score < 2.6 was maintained in both APR treatment groups (21.3% [36/169] in the 20mg group and 20.4% [34/167] in the APR 30mg arm). By comparison, the distribution of DAS 28 (CRP) score did not appreciably change over time from baseline in the PBO-treated subjects. At baseline, more than half of all subjects had a CDAI score > 22. Therapy with APR had a positive effect on CDAI scores as indicated by the proportion of subjects with high disease activity at baseline which decreased by week 16, and the percentage of subjects with disease remission or low disease activity at week 16 compared to baseline. The proportion of subjects with high disease activity that decreased from baseline to week 16 was 55.0% (93/169) to 37.9% (64/169) for APR 20mg subjects and 56.3% (94/167) to 31.1% (52/167) for APR 30mg patients. The proportion of subjects with low disease activity increased from baseline to week 16 - 3.0% (5/169) to 17.8% (30/169) for APR 20mg subjects and 1.2% (2/167) to 24.6% (41/167) for APR 30 mg patients. These effects were maintained at week 24.

Among subject with enthesitis at baseline, APR treatment (both doses) produced numerically similar LS mean reduction (improvement) in the MASES score at week 16 and 24 compared to PBO, and none of the treatment comparisons between APR and PBO were statistically significant. For the PBO group, the LS mean reduction in MASES score at both week 16 and 24 was -0.7 (baseline mean score 4.4). For the APR 20mg arm, the LS mean reduction in MASES score at week 16 was -0.7, and at week 24 was -1.0 (baseline mean score 4.4). For the APR 30mg group, the LS mean reduction in MASES score at week 16 was -1.0, and at week 24 was -1.1 (baseline mean score 4.4). Among subjects with pre-existing dactylitis, APR treatment (both doses) produced a numerically greater LS mean reduction (improvement) in the dactylitis score at week 16 and 24 compared to PBO, but only the comparison between APR 30mg and PBO at week 24 was statistically significant. For the PBO group, the LS mean reduction in the dactylitis score at both week 16 and 24 was -1.3 (baseline mean score 3.9). For the APR 20mg arm, the LS mean reduction in the dactylitis score at both week 16 and 24 was -1.7 (baseline mean score 3.7). For the APR 30mg group, the LS mean reduction in the dactylitis score at week 16 was -2.1, and at week 24 was -2.3 (baseline mean score 4.1).

Subjects treated with APR achieved statistically significant ($p < 0.05$) LS mean improvements (increases) from baseline in the SF-36 Physical Functioning domain score at week 16 compared with PBO. The improvements were dose-dependent and maintained at week 24. The LS mean improvement in the APR 20mg group was 2.3 points at week 16 and 2.7 points at week 24 (baseline mean of 34.7). For the APR 30mg treatment group, the LS mean improvements were 3.5 points at 16 weeks and 3.4 points at 24 weeks (baseline mean of 37.9). In the control arm, the LS mean improvement at week 16 was 1.1 points, and 1.0 points at week 24 (baseline mean of 35.5). Subjects in the APR 30mg treatment group recorded a statistically greater ($p = 0.0049$) mean improvement (increase from baseline) in the FACIT-F score at week 16 compared with PBO, which was maintained at week 24 ($p = 0.0078$). The LS mean improvement observed in the APR 30mg group at week 16 was 3.72 points, and at week 24 was 3.27 points (baseline mean

score 28.6). No differences in FACIT-F scores were observed between the APR 20mg treatment group (1.86 points at week 16 and 2.01 points at week 24; baseline mean 30.0) and PBO at week 16 or 24 (1.18 points at week 16 and 0.83 points at week 24; baseline mean 28.9).

Statistically greater proportions of subjects in both APR treatment groups achieved a PASI 75 response at week 16 compared with PBO (20.9% [19/91] in the 20mg group and 22.2% [20/90] in the 30mg arm versus 7.9% [7/89] in the PBO group, respectively; p = 0.0134 and p = 0.0062, respectively). These improvements were maintained at week 24, but only the improvement for the APR 30mg treatment group was statistically significant (22.2% [20/91] in the 20mg group and 25.6% [23/90] in the 30mg arm, respectively, versus 11.2% [10/89] in the PBO group; p = 0.0515 and 0.0099, respectively). A dose effect with APR was observed for the skin response. This was an important secondary efficacy endpoint in Study PSA-004 which specifically recruited subjects with active PSOR at baseline.

At week 52 (observed data), the rate of modified ACR20 response was 56.0% (65/116) in the APR 20mg group and 63.0% (80/127) in the APR 30mg arm. Improved physical functioning, as measured by the LS mean change from baseline in the HAQ-DI score continued up to week 52. The improvement in the LS mean HAQ-DI score observed in the APR 20mg was -0.332 and -0.350 in the APR 30mg treatment group. All other efficacy endpoints consistently demonstrated sustained benefit with APR therapy (either dose regimen) up to week 52.

7.1.1.1.13.4. Study PSA-005

Regarding the key secondary efficacy endpoint of the LS mean change from baseline to week 16 in the HAQ-DI score, subjects treated with APR had statistically significantly greater improvements (reductions) compared with PBO. The LS mean changes in the HAQ-DI score at week 16 were -0.156 for the APR 20mg group and -0.205 for the APR 30mg arm versus 0.012 in the PBO group (p = 0.0008 and p < 0.0001, respectively). These improvements were maintained at week 24 for both APR treatment groups (-0.156 and -0.207, respectively, versus 0.012 in the PBO group; p = 0.0014 and p < 0.0001). An APR dose regimen effect was observed for this efficacy outcome in addition to the rate of modified ACR20 response at week 16. The proportion of subjects achieving the HAQ-DI MCID change of -0.3 units at weeks 16 and 24 was higher in the APR treatment groups (36.0% [63/175] at week 16 and 36.6% [64/175] at week 24 for the 20mg group and 34.7% [61/176] at week 16 and 33.0% [58/176] at week 24 for the APR 30mg arm) compared with PBO (19.3% [34/176] at week 16 and 18.2% [32/176] at week 24; nominal p-value <0.002 for all pair-wise comparisons).

At week 24, a statistically greater proportion of patients treated with APR achieved a modified ACR20 response (29.1% [51/175] for the 20mg group and 24.4% [43/176] for the 30mg arm) compared with PBO (13.1% [23/176]; p = 0.0002 and p = 0.0063, respectively) (Table 12).

Table 12: Proportion of Subjects Achieving ACR20 Response at Week 24 and ACR50/70 Response at Weeks 16 and 24 in Study PSA-005

Endpoint	Placebo N = 176	APR 20 BID N = 175	APR 30 BID N = 176
Number (%) of ACR 20 responders at Week 24	23 (13.1)	51 (29.1)	43 (24.4)
Treatment comparison (apremilast – placebo)			
Treatment difference in proportions (95% CI)[a]	--	16.1 (7.7, 24.4)	11.4 (3.3, 19.4)
2-sided p-value[b]	--	**0.0002**	**0.0063**
Number (%) of ACR 50 responders at Week 16	8 (4.5)	20 (11.4)	20 (11.4)
Treatment comparison (apremilast – placebo)			
Treatment difference in proportions (95% CI)[a]	--	6.9 (1.3, 12.5)	6.8 (1.2, 12.4)
2-sided nominal p-value[b]	--	*0.0173*	*0.0181*
Number (%) of ACR 70 responders at Week 16	2 (1.1)	7 (4.0)	7 (4.0)
Treatment comparison (apremilast – placebo)			
Treatment difference in proportions (95% CI)[a]	--	2.9 (-0.4, 6.2)	2.8 (-0.4, 6.1)
2-sided nominal p-value[b]	--	0.0897	0.0913
Number (%) of ACR 50 responders at Week 24	11 (6.3)	28 (16.0)	22 (12.5)
Treatment comparison (apremilast – placebo)			
Treatment difference in proportions (95% CI)[a]	--	9.8 (3.2, 16.3)	6.3 (0.2, 12.3)
2-sided nominal p-value[b]	--	*0.0037*	*0.0443*
Number (%) of ACR 70 responders at Week 24	7 (4.0)	7 (4.0)	8 (4.5)
Treatment comparison (apremilast – placebo)			
Treatment difference in proportions (95% CI)[a]	--	0.0 (-4.1, 4.1)	0.6 (-3.7, 4.8)
2-sided nominal p-value[b]	--	0.9913	0.7919

ACR 20/50/70 = American College of Rheumatology 20%/50%/70% response; APR = apremilast; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; NRI = nonresponder imputation.

[a] Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

[b] Two-sided p-value is based on the chi-square test. P-values in bold are considered statistically significant. P-values in italics are ≤ 0.050 and are considered nominally significant as hierarchical testing was stopped after secondary endpoint #6 for the APR 20 BID treatment group and after secondary endpoint #7 for the APR 30 BID treatment group (rules described in Section 11.4.2.5).

A greater proportion of subjects in the APR 20mg and APR 30mg treatment groups compared with PBO achieved ACR50 response at week 16, which was maintained at week 24. However, no notable differences were observed between the APR treatment groups (either dose) and PBO for the rate of ACR70 response at either week 16 or week 24.

The majority of secondary endpoints supported the efficacy of APR in the improvement of both the signs and symptoms, and physical functioning in subjects with active PsA. APR therapy produced modified PsARC response rates at week 16 that were statistically higher in the APR 20mg (38.9% [68/175]; p = 0.0037) and APR 30mg treatment group (45.5% [80/176]; p < 0.0001) compared with PBO (24.4%; 43/176). The responses were maintained at week 24 (36.6% [64/175] for APR 20mg and 35.2% [62/176] for APR 30mg) versus the PBO group (17.0% [30/176]; p < 0.0001 for both comparisons). Consistent with these observations, the proportion of subjects obtaining a good or moderate EULAR response at week 16 was higher in the APR 20mg (42.9% [75/175]; p = 0.0013) and APR 30mg (44.9% [79/176]; p = 0.0001) treatment groups compared with PBO (25.0%; 44/176). Good or moderate EULAR response was maintained at week 24 in the 2 APR treatment groups (48.0% [84/175] in the 20mg group and 43.2% [76/176] in the 30mg arm) compared to PBO (26.1% [46/176]; p < 0.011 for both comparisons). The proportion of subjects reaching CDAI score of ≤ 10 (indicating low disease activity or remission) was also higher in the APR treatment groups compared with PBO at both weeks 16 and 24. At week 16, the proportion of subjects in each treatment group with CDAI of 10 or less was 20.6% (36/175) in the APR 20mg group and 20.5% (36/176) in the APR 30mg

arm versus 11.9% (21/176) in the PBO group. At 24 weeks, the proportion of subjects in each treatment group with CDAI of 10 or less was 21.7% (38/175) in the APR 20mg group and 18.2% (32/176) in the APR 30mg arm versus 10.8% (19/176) in the PBO group.

A treatment effect for APR on enthesitis was observed in the APR 30mg treatment group in subjects with pre-existing enthesitis. The decrease from baseline (improvement) in the MASES score relative to PBO was statistically significant at week 16 (-1.5 for APR 30mg versus -0.5 for PBO; p = 0.0038) and week 24 for the APR 30mg treatment group (-1.5 for APR 30mg versus -0.6 for PBO; p = 0.0114). However, no significant differences in the change from baseline in the MASES were observed between the PBO and APR 20mg treatment group at either week 16 (-0.5) or 24 (-0.9). A treatment effect for APR on dactylitis was also shown. The decrease from baseline (improvement) in the dactylitis severity score relative to PBO was shown in the APR 20mg group at weeks 16 (-1.0 versus -1.9; p = 0.0112) and 24 (-1.0 versus -2.0; p = 0.0074), and also in the APR 30mg arm at week 16 (-1.7 at both time points; p = 0.0476 at week 16).

A positive treatment and dose effect for APR on the rate of PASI 75 response was observed at weeks 16 and 24 in subjects with PSOR involving ≥ 3% BSA at baseline. The PASI 75 responses at week 16 were 10.8% (10/93) in the PBO group versus 17.3% (18/104; p = 0.1884) in the APR 20mg arm and 26.6% (29/109; p = 0.0044) in the APR 30mg group. The PASI 75 responses were improved or maintained in the APR treatment groups at week 24 (23.1% [24/104]; p = 0.0392 in the 20mg group and 25.7% [28/109]; p = 0.0129 in the 30mg arm) compared with 11.8% (11/93) in the PBO group.

Treatment related improvements with APR were observed at both weeks 16 and 24 in the SF-36 physical functioning domain score and PCS score. At week 16, the LS mean change from baseline in the SF-36 physical functioning domain score improved from baseline by 0.01 (baseline 35.8), 2.39 (baseline 35.5; p = 0.0043) and 3.19 (baseline 35.7; p = 0.0002) in the PBO, APR 20mg and APR 30mg treatment groups, respectively. Similarly, the LS mean change from baseline in the SF-36 PCS scores improved by 0.93 (baseline 35.85), 3.15 (baseline 35.6; p = 0.0034) and 4.20 (baseline 36.3; p < 0.0001) in the PBO, APR 20mg and APR 30mg treatment groups, respectively. The mean improvements in the SF-36 physical functioning domain and PCS scores at week 16 were maintained at week 24 in all of the treatment groups. The LS mean difference in the increase from baseline (improvement) in the FACIT-F score between APR 30mg and PBO was significant at both weeks 16 (mean improvement of 2.62 [baseline 30.66] versus 0.07 [baseline 31.60]; p = 0.0045) and week 24 (mean improvement of 2.58 versus 0.25; p = 0.0120). However, there was no significant difference between the APR 20mg group and PBO at either week (mean change of 1.19 at week 16 and 1.37 at week 24 from a baseline score of 31.72). Study PSA-005 did not collect DLQI scores for assessment.

7.1.2. Other efficacy studies

7.1.2.1. Study PSA-001

7.1.2.1.1. Study design, objectives, date and locations

Study PSA-001 was a double-blind, randomized, placebo-controlled, parallel-group, Phase II proof-of-concept study evaluating the efficacy and safety of 2 doses of APR in adult patients with active PsA. It was conducted between March 2007 and May 2009 at 38 sites in Canada, Belgium, Germany, Netherlands and the United Kingdom. The primary objective of Study PSA-001 was to evaluate the clinical efficacy of orally administered APR (20mg twice daily or 40mg once daily) on the signs and symptoms of active PsA at 84 days (12 weeks). The trial consisted of a pre-randomisation phase of up to 35 days followed by a 12-week treatment period (randomized 1:1:1 to APR 20mg twice daily, APR 40mg once daily or PBO), and then after global protocol amendment 1 an extension phase of up to 12 weeks (with continued treatment blinding). In the extension phase, subjects receiving either dose regimen of APR in the treatment period remained on the same regimen, while subjects in the PBO group were re-randomized 1:1 to either APR 20mg twice daily or 40mg once daily. In addition, there was a 4-week observational

follow-up period for subjects completing either the treatment or extension phase, or for those who prematurely discontinued at any time point. Efficacy assessments were performed at baseline and every 2 weeks during the 12-week initial treatment period, and every 4 weeks during the extension phase.

Six protocol amendments were implemented at 2 time points after the study commenced. The amendments contained clarifications about baseline assessments, efficacy measures and minor safety related issues. Three of the changes with global amendment 1 (31 October 2007) are noteworthy: (1) extending the blinded treatment duration with APR from 12 to 24 weeks, (2) PBO subjects completing the initial 12 week treatment phase were to be re-randomised at this time point to receive 1 of the APR dose regimens in the extension phase and (3) PBO subjects switched over to APR at week 12 were to receive dose titration of APR between days 85 - 91.

7.1.2.1.2. Inclusion and exclusion criteria

Study PSA-001 enrolled subjects > 18 years of age with a documented diagnosis of PsA for at least 6 months duration, according to the Moll and Wright criteria, as well having a negative rheumatoid factor blood test. Subjects had to have active disease at the time of screening and baseline defined as ≥ 3 swollen and ≥ 3 tender joints. Patients taking MTX were eligible for inclusion if they had been taking MTX for at least 24 weeks (stable dose for at least 56 days) prior to screening. These subjects continued stable dose MTX during the trial. If patients were using oral CS, this must have been stable at dose of prednisone < 10 mg/day for at least 28 days prior to screening, and maintained throughout the study. Concurrent NSAID was also permissible if stable for at least 14 days prior to screening.

The exclusion criteria were highly similar to the Phase III PsA Studies in terms of excluded medical co-morbidity, abnormal laboratory tests and current and prior treatment exposures.

7.1.2.1.3. Efficacy endpoints and statistical plan

The primary efficacy endpoint of the study was the number of subjects who achieved an ACR20 response at day 85 (i.e. at the final week 12 treatment visit). The secondary efficacy endpoints of the trial (assessed at day 85 and day 169) were the proportion of subjects in each treatment group obtaining ACR50 response, ACR70 response, PsARC; percentage of patients with or without dactylitis and/or enthesitis; and the mean change from baseline in the SF-36, DLQI, HAQ-DI and FACIT-F scores. All efficacy analyses were conducted on the Intention-to-Treat (ITT) population, which consists of all randomized subjects with at least 1 of the ACR components assessed at baseline.

The primary endpoint (proportion of subjects who achieved ACR20 response at week 12) was analysed for each of the 2 APR treatment groups (20mg twice daily and 40mg once daily) compared with PBO in a pair-wise manner using the continuity corrected chi-square test. The 95% two sided CI for the odds ratio was determined. As a sensitivity analysis for ACR20 response, the CMH test controlling for MTX use was also used to compare each APR treatment group to PBO. No procedures to maintain the overall type 1 error at 0.05 level were planned or conducted for the secondary endpoints. The Kaplan-Meier procedure was used to characterise time to achieve clinically relevant changes such as the ACR20 response.

Based on a literature review, a clinically relevant difference in the ACR20 response rate between subjects on active treatment versus PBO at day 85 would be 25% (i.e. 20% of the subjects in the PBO group would improve and 45% in the APR arm would improve). A 2-group chi-square test with a 0.05 one-sided significance level would have 80% power to detect a 25% difference between treatment groups when the sample size in each group is 51. If 25% of all subjects discontinued during the trial, 68 subjects were estimated to be enrolled into each of the 3 treatment groups (i.e. total of 204 subjects).

7.1.2.1.4. Subject disposition and protocol violations

A total of 204 subjects with active PsA were enrolled and randomized in this trial: 68 to placebo, 69 to APR 20mg twice daily and 67 to APR 40mg once daily. Of these 204 subjects, 165 (80.9%) completed 12 weeks of treatment follow-up. A higher proportion of subjects in the APR 40mg group completed the 12 week treatment phase (89.6%; 60/67) compared with APR 20mg (79.7%; 55/69) and PBO (73.5%; 50/68) The most common reasons for premature discontinuation in the 39 subjects were AEs (6.9%; 14/204) and worsening or not responding to study medication (8.8%; 18/204).

Of the 165 subjects who completed the initial 12-week treatment phase, 126 chose to enter the extension period (46 in the APR 40mg group, 40 in the APR 20mg arm and 40 from the PBO group [20 patients were randomised to each of the APR dose regimens) and 103 patients completed the extension phase (76.1% [35/46] in the APR 40mg group, 90% [36/40] in the APR 20mg arm, 95% [19/20] in the APR 40mg crossover cohort and 65% [13/20] in the APR 20mg crossover group). Similar to the 12-week data, the most common reasons for premature discontinuation in the extension phase were AEs (4.8%; 6/126) and worsening or not responding to study medication (6.4%; 8/126).

A total of 15 major (7.4% of 204) and 50 minor (24.5% of 204) protocol deviations were recorded in Study PSA-001. Protocol deviations were equally distributed among the 3 treatment groups in terms of incidence, type and severity. The major protocol violations included 4 subjects who stopped or modified their NSAID therapy, 4 patients who had violations of the inclusion/exclusion criteria, 3 subjects who took additional NSAID treatment, 2 subjects who received intra-articular CS injections, a patient with competing musculoskeletal pain from spinal canal stenosis and a subject in the APR 40mg group who was non-compliant with study treatment (< 60% drug adherence).

7.1.2.1.5. Baseline data

Overall, subjects had a mean age of 50.6 years (range: 21 - 81 years), just over half (52.5%; 107/204) were male, and the majority (96.6%; 197/204) were of Caucasian ethnicity. The majority of subjects (52.9%; 108/204) had a BMI of between 18.5 and 29.9 kg/m2, but obesity (30-34.9 kg/m2) and morbid obesity (> 35 kg/m2) was also common (27.9% [57/204] and 18.6% [38/204], respectively). One quarter (20.6%; 42/204) of all subjects were current tobacco users and approximately two thirds of patients came from Europe (67.2%; 137/204). In general, the treatment groups were well balanced with respect to demographic characteristics although patients in the APR 20mg twice daily group were more likely to be > 65 years of age (20.3% versus 7.5% in the other 2 groups), male (62.3% versus 47.5%) and had a lower rate of obesity (28.9% versus 51% in the other 2 arms).

The treatment groups were similar with respect to baseline PsA features. The mean duration of PsA for all subjects was 7.8 years (median 5.3 years, range: 0.0 - 43.3 years). A longer median duration of PsA was observed in the PBO group (6.4 years) compared to the APR arms (4.7 and 4.8 years). Expectedly, the median duration of psoriasis was substantially longer in all of the treatment groups (overall 13.3 years). The subtype of PsA (as defined by the investigator) was recorded at baseline. The majority of patients had either symmetrical polyarthritis (52.5%; 107/204) or asymmetrical oligoarthritis (32.8%; 67/204). Asymmetric oligoarthritis affected a higher percentage of APR 40mg enrolled subjects (38.8%; 26/67) compared to the other 2 groups (29.4 - 30.4%) Most patients had mild or moderate severity skin psoriasis at baseline (62.7% [128/204] and 22.5% [46/204], respectively) and this was recorded at a similar frequency between the 3 treatment arms.

In terms of PsA disease activity at baseline, the mean numbers of tender and swollen joints were similar for all 3 treatment groups (21.7 and 9.5, respectively). The mean HAQ-DI scores were similar between the 3 treatment groups at 1.22 - 1.24, and consistent with moderate disease

activity. The median baseline CRP readings were similar in the APR treatment groups (5.0 - 5.1 mg/dL) but higher in the PBO arm at 7.6 mg/dL.

Overall, the majority of subjects had received previous DMARD treatment with MTX (64.7%; 132/204) and SSZ (23.5%; 48/204). The pattern of prior DMARD use was similar in each of the treatment groups. The majority of patients (81.4%; 166/204) in all treatment groups had a past history of taking NSAIDs, and one fifth (20.6%; 42/204) of subjects had previously taken low dose oral CS. Regarding prior exposure to biologic DMARDs – 22 subjects (10.8%) had previously used etanercept and 12 patients (5.9%) had previously used infliximab. During the study, 42.2% (86/204) of all patients took concurrent MTX at a very broad range of doses (1.5-30 mg/week). Use of concomitant MTX was lower in the PBO group (38.2%; 26/67) compared to the APM treatment groups (44.8% [30/62] in the 40mg arm and 43.5% [30/67] in the 20mg cohort). The median weekly dose of concurrent MTX used in all 3 groups was 15.0 mg (mean 15.7 - 16.5 mg; range: 7.5 - 25mg). In addition, approximately one third of all patients (36.8%; 75/204) took concomitant NSAID during the trial, and 6.9% (14/204) of subjects took low dose oral CS.

The incidence of relevant co-morbid conditions was similar in the treatment groups. A past history of hypertension was recorded in 33.3% of all subjects (68/204) and 8.8% (18/204) reported hyperlipidaemia. Past history of depression was recorded in 12.7% of patients (26/204).

7.1.2.1.6. Efficacy results

At week 12, both APR treatment arms had a significantly greater proportion of subjects achieving an ACR20 response: 35.8% (24/67) of subjects in APR 40mg once daily group and 43.5% (30/69) of subjects in the APR 20mg twice daily arm compared to 11.8% (8/68) of patients in the PBO group ($p = 0.002$ and $p < 0.001$, respectively). Separation of the ACR20 response rates between the active APR and placebo arms was seen as early as week 4 and continued through to week 12. Sensitivity analyses performed using subjects who had at least 1 post-baseline ACR assessment with different rules for handling of missing data, as well as using the PP population, confirmed the primary efficacy analysis result. Treatment benefit with APR was preserved across all the subgroup features of interest, including concurrent MTX use (yes/no), apart from PsA subtype. Subjects with asymmetric oligoarthritis on either dose regimen of APR (53.2%; 25/47) demonstrated a higher rate of ACR20 response at week 12 than those with symmetric polyarthritis (26.5%; 18/68). During the extension phase, 40 - 45% of subjects in each of the 4 treatment groups (original and crossover APR subjects - both dose regimens) achieved an ACR20 response at week 24 (day 169). In the PBO crossover subjects who achieved an ACR20 response, > 90% of these patients were observed to reach ACR20 response soon after switching to APR (i.e. at 4 - 8 weeks after the treatment change).

At 12 weeks, significantly more subjects in the APR 20mg twice daily treatment group achieved an ACR50 response at day 85 compared with placebo (17.4% [12/69] versus 2.9% [2/68], respectively; $p = 0.012$). However, the ACR50 response rate in the APR 40mg once daily arm was not statistically superior to placebo (13.4% [9/67] versus 2.9%; $p = 0.056$). There was no statistical difference between either APR treatment group (7.5% [5/67] for 40mg once daily and 5.8% [4/69] for 20mg twice daily) and control (1.5%; 1/68) for the rate of ACR70 response at 12 weeks. The percentage of patients achieving an ACR50 and ACR70 response during the extension phase in the 2 original APR treatment groups as well as the APR PBO to 40mg once daily group were similar (20 - 24% for ACR50 and 13 - 17.5% for ACR70 response rate) but numerically lower in the PBO to APR 20 mg twice daily crossover group (15% [3/20] for ACR50 and 5% [1/20] for ACR70 response).

Consistent with the ACR20 response rate data, the rate of achieving PsARC at 12 weeks was higher in both APR treatment groups (50.7% [34/67] for 40mg once daily and 52.2% [36/69] for 20mg twice daily) compared with the placebo arm (22.1%; 15/68). During the treatment

phase, the proportion of patients with active enthesitis on either the left or right side of the Achilles tendon at insertion into the calcaneus decreased in all 3 treatment groups from baseline to week 12: 22.4% to 20.9% in the APR 40mg once daily group, 21.7% to 17.4% in the APR 20mg twice daily arm and 35.3% to 17.6% in the PBO group. However, at the plantar fascia insertion into the calcaneus, the percentage of subjects with active enthesitis on either side decreased in both APR groups (26.9% to 19.4% in the 40mg group and 26.1% to 21.7% in the 20mg cohort) but increased in the PBO arm (14.7% to 17.6%). In the extension phase, the proportion of subjects with enthesitis at either anatomical location stayed the same for both APR groups that continued on their baseline treatment allocation, but increased by 20% in the PBO to APR 40mg crossover group and decreased by 5% in the PBO to APR 20mg crossover cohort. Few subjects had dactylitis at baseline so it was difficult to measure the change in this efficacy endpoint at week 12 or 24.

The mean change from baseline to week 12 in the HAQ-DI score was not statistically significant in either APR treatment group (-0.2 for both arms) versus PBO (-0.1 mean change). During the initial 12-week treatment period, there was a statistically significant mean improvement from baseline in the SF-36 MCS and PCS scores in the APR 20mg twice daily group (3.4 point improvement for MCS and 2.4 point improvement for PCS) compared to PBO (0.8 point decline for MCS and 0.8 point improvement for PCS) but the mean change seen in the APR 40mg group did not reach statistical significance compared to PBO (1.0 point improvement in MCS and 2.1 point improvement in PCS). During the extension phase (weeks 12 - 24), patients in all 4 treatment groups showed significant mean improvements from baseline in the PCS score (3.2-4.4 point improvements) but not the MCS scores (ranging from -2.7 to 1.4 point mean changes). During the initial treatment phase, there was a statistically significant mean improvement from baseline in the FACIT-F scores in both APR treatment groups (4.3 point improvement from baseline score of 27.7 in the 40mg group, and 4.1 point improvement from baseline score of 32.1 in the 20mg arm) compared to PBO (0.5 point improvement from baseline score of 28.8; $p = 0.028$ and $p = 0.004$, respectively). Of the subjects that entered the extension phase, those that remained on APR (either regimen) maintained their mean improvement in FACIT-F score, while the crossover subjects (either regimen) did not show a significant improvement from baseline. During the initial 12-week treatment period, there was a statistically significant mean improvement from baseline in the DLQI score in the APR 40mg once daily group (2.6 point improvement from baseline score of 7.7) compared to PBO (0.3 point improvement from baseline score of 7.1; $p = 0.016$) but the mean change seen in the APR 20mg twice daily group did not reach statistical significance compared to PBO (1.8 point improvement from baseline score of 5.3; $p = 0.105$).

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

The submission contained a comparison and analysis of the results across the 3 pivotal Phase III studies in PSA which enrolled subjects with prior and/or concomitant DMARD therapy (Studies PSA-002, PSA-003 and PSA-004), but no pooled analysis of the results was provided. The comparison did not reveal any new observations than that demonstrated in the individual trials.

All 3 of the prior and/or concomitant DMARD use Phase III PsA trials (Studies PSA-002, PSA-003 and PSA-004) demonstrated a statistically significant difference between PBO and the individual APR treatment arms (20mg and 30mg twice daily) for the primary efficacy outcome (i.e. the rate of modified ACR20 response at week 16). The sponsor is proposing licensing of only the 30mg twice daily dose regimen, however, only 1 of these 3 trials (PSA-004) demonstrated statistical superiority for 30mg versus 20mg twice daily. In fact, Study PSA-003 showed the 20mg dose regimen was numerically better than the 30mg regimen, but this observation was not statistically confirmed).

Subgroup analyses of the modified ACR20 response rate at week 16 in Studies PSA-002, PSA-003 and PSA-004 demonstrated that the favourable treatment effect with APR versus PBO was observed irrespective of PsA subtype, prior use of conventional or biologic DMARD use, or

concomitant conventional DMARD use (approximately 35% of all subjects received APR monotherapy and 65% took APR in combination with conventional DMARDs). Table 13 provides a detailed summary of prior and concomitant DMARD use in the 3 Phase III PsA studies in which such medicines could be used.

Table 13: Prior and Concomitant Medication Use in Studies PSA-002, PSA-003 and PSA-004.

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR20 BID N=168	APR30 BID N=168	PBO N=159	APR20 BID N=163	APR30 BID N=162	PBO N=169	APR20 BID N=169	APR30 BID N=167
Any Prior DMARDs used[a]; n (%)	161 (96)	166 (99)	165 (98)	158 (99)	163 (100)	157 (97)	169 (100)	168 (99)	167 (100)
DMARDs used[a]; n (%)									
Methotrexate	140 (83)	141 (84)	140 (83)	138 (87)	141 (87)	137 (85)	151 (89)	139 (82)	142 (85)
Sulfasalazine	43 (26)	51 (30)	43 (26)	62 (39)	62 (38)	47 (29)	39 (23)	30 (18)	46 (28)
Leflunomide	22 (13)	23 (14)	26 (16)	33 (21)	32 (20)	34 (21)	20 (12)	27 (16)	20 (12)
Other[b]	57 (34)	52 931)	59 (35)	31 (20)	44 (27)	47 (29)	62 (37)	68 (40)	56 (34)
Prior Biologic Use[a]; n (%)	41 (24)	37 (22)	41 (24)	23 (15)	28 (17)	23 (14)	48 (28)	50 (30)	43 (26)
Biologic used[a]; n (%)									
TNFi	39 (23)	33 (20)	37 (22)	20 (13)	27 (17)	22 (14)	45 (27)	48 (28)	39 (23)
non-TNFi	9 (5)	9 (5)	8 (5)	4 (3)	6 (4)	7 (4)	8 (5)	11 97)	7 (4)
Prior Biologic Failure; n (%)	19 (11)	14 (8)	14 (8)	8 (5)	10 (6)	7 (4)	12 (7)	18 (11)	14 (8)
Concomitant PsA Treatment at Baseline									
DMARD use; n (%)	110 (66)	111 (66)	106 (63)	113 (71)	114 (70)	113 (70)	101 (60)	104 (62)	101 (61)
Oral Corticosteroids; n (%)	12 (7)	25 (15)	16 (10)	20 (13)	36 (22)	25 (15)	16 (10)	34 (20)	23 (14)
NSAIDs; n (%)	118 (70)	123 (73)	120 (71)	108 (68)	115 (71)	114 (70)	115 (68)	121 (72)	121 (73)
Opioids/Analgesics; n (%)	27 (16)	32 (19)	25 (15)	22 (14)	22 914)	22 (14)	18 (11)	20 (12)	24 (14)

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg; PsA: psoriatic arthritis; TNFi: tumor necrosis factor inhibitor DMARD: disease modifying anti-rheumatic drug; NSAID:

Regarding the key secondary efficacy endpoint of the LS mean change from baseline to week 16 in HAQ-DI score, a statistically significant and clinically meaningful improvement (reduction) was seen in the APR 30mg twice daily treatment groups in all 4 pivotal PsA trials (despite prior treatment with conventional and/or biologic DMARDs in 3 of those trials), and in the APR 20mg twice-daily treatment group in 3 of the studies (PSA-002, PSA-003 and PSA-005). An APR dose effect was observed in all 4 pivotal PsA studies.

7.1.4. Evaluator's conclusions on clinical efficacy for indication 1: Treatment of active psoriatic arthritis in adult patients

The primary dataset used for assessing the efficacy of APR in adult subjects with active PsA involved 4 Phase III studies. In this submission, 3 of the Phase III studies (PSA-002, PSA-003 and PSA-004) submitted a 52-week efficacy report, and Study PSA-005 submitted a 24-week efficacy report. Studies PSA-002, PSA-003 and PSA-004 were highly similar in design and conduct except that Study PSA-004 enrolled subjects with PSOR at baseline and additionally assessed skin response as a secondary endpoint. Study PSA-005 evaluated APR as a monotherapy, whereas the 3 other Phase III trials assessed APR as either monotherapy or in combination with conventional DMARDs. All of the studies were designed as 24-week, randomized, PBO-controlled, double-blind, parallel group, multi-centre studies conducted in patients 18 years of age or older with active PsA (defined as 3 or more tender and swollen joints at baseline in accordance with CASPAR criteria). In all 4 Phase III studies, subjects in the PBO arm were allowed to enter early escape to active treatment with APR in a blinded manner if failing to sufficiently respond by week 16, hence, the true PBO-controlled study periods were 16 weeks in duration. In each of the 4 Phase III trials, subjects were randomized in a 1:1:1 ratio to receive oral treatment with APR 20mg twice daily, APR 30mg twice daily, or matching PBO tablets. In 3 of the 4 pivotal studies, treatment assignments were stratified based on conventional DMARD use, and the enrolment of patients with a documented treatment failure to anti-TNF drugs was limited to < 10% of all subjects. The sponsor is only seeking approval of the APR 30mg twice daily posology.

The primary efficacy endpoint used by all 4 Phase III studies was the proportion of subjects achieving a ≥ 20% improvement of the ACR response criteria at week 16. The ACR20 endpoint was modified for PsA by the addition of the DIP joints of the toes and carpometacarpal joints to the total joint counts (78 tender joints and 76 swollen joints). The major secondary endpoint for all 4 studies was the assessment of APR on physical function as measured by the LS mean change from baseline in the HAQ-DI score at week 16. Both of these endpoints have been validated and used in previous approvals of other drugs indicated for patients with active PsA, and are accepted by international peer groups. The ACR criteria for assessing disease activity includes several subjective assessments susceptible to bias, but in all of the trials appropriate blinding of investigators and subjects was undertaken. This submission is seeking an indication in active PsA, and in general is consistent with the TGA adopted regulatory guideline pertaining to the requested extension of indication: EMEA guideline CPMP/EWP/438/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis" (effective 5 February 2008). In the Phase III trials, the choice of clinical (joints and skin), physical functioning and QOL endpoints, as well as the statistical analysis were appropriately performed.

The baseline demographic and disease related characteristics of patients in each of the 4 studies are similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. However, there are some caveats to the generalizability of the treatment population. For example, all of the trials excluded patients who were at a significant risk of infection, or who had various abnormal laboratory results at baseline (e.g. abnormal haematology or liver function tests).

Analysis of the primary endpoint for Studies PSA-002, PSA-003 and PSA-004 demonstrated a statistically greater proportion of APR 30mg (32.1 - 40.7%; $p < 0.0060$ for all comparisons) and APR 20mg (28.4 - 37.4%; $p < 0.0295$ for all comparisons) treated subjects achieved a modified ACR20 response at week 16 compared to PBO-treated subjects (18.3 - 19.0%). Results for the ACR50 and ACR70 response rate at week 16 were consistent with the ACR20 data. Efficacy results generally supported a greater numerical advantage for the APR 30mg twice daily regimen compared to the APR 20mg twice daily posology, but there were limited statistically significant analyses to support the conclusion that APR 30mg twice daily was superior to APR 20mg twice daily. Study PSA-004 demonstrated statistical superiority for 30mg versus 20mg twice daily for the rate of ACR20 response at week 16, and Study PSA-003 showed the 20mg dose regimen was numerically better than the 30mg regimen, but this latter observation was not statistically confirmed.

APR treatment (both dose regimens) was also associated with an improvement in the HAQ-DI score from baseline, and the majority of pair-wise comparisons between APR and PBO reached statistical significance. The treatment effect size for APR 30mg twice daily for the LS mean change in HAQ-DI from baseline to week 16 ranged from -0.19 to -0.24 versus -0.05 to -0.09 for PBO-treated subjects. For the APR 20mg twice daily treated subjects the LS mean change in HAQ-DI from baseline to week 16 ranged from -0.13 to -0.20. Several other secondary efficacy measures examining other clinical outcomes (e.g. PsARC response; as well as PASI response in Study PSA-004) and health related QOL endpoints (physical function domain scores of SF-36 and mean change from baseline in FACIT-F score) also demonstrated improvements with APR. However, in most of the Phase 3 studies APR 30mg twice daily produced numerically greater improvements in enthesitis and dactylitis scores, but often the difference did not achieve statistical superiority compared with PBO. In the pivotal Phase 3 studies, clinical response was maintained for up to 52 weeks of treatment but observations taken after 24 weeks were not PBO controlled.

Although the Phase III studies were not designed to compare the efficacy of concomitant DMARD, or that of anti-TNF experienced versus anti-TNF naïve groups, APR demonstrated superior efficacy compared to PBO regardless of concurrent DMARD use and, importantly among the majority of anti-TNF experienced patients.

Study PSA-005 was different from the other 3 Phase III trials in that it enrolled subjects who were DMARD naïve, and concomitant DMARD therapy was prohibited during the study. The results of this trial showed a similar rate of ACR20 response at weeks 16 (28.0 - 30.7%) and 24 (24.4 - 29.1%) with both doses of APR, but the 30mg twice daily regimen demonstrated a greater treatment effect compared with APR 20mg twice daily for the LS mean change from baseline in HAQ-DI score at weeks 16 and 24 (-0.156 versus -0.207).

The supporting Study PSA-001 supported the observation that APR therapy (20mg twice daily and 40mg once daily) results in clinically meaningful improvements in joint disease activity. It assessed the primary efficacy outcome at 12 weeks (rate of ACR20 response) but continued collecting data in an extension phase. At week 12, both APR treatment arms had a significantly greater proportion of subjects achieving an ACR20 response: 35.8% (24/67) of subjects in APR 40mg once daily group and 43.5% (30/69) of subjects in the APR 20mg twice daily arm compared to 11.8% (8/68) of patients in the PBO group ($p = 0.002$ and $p < 0.001$, respectively). Separation of the ACR20 response rates between the active APR and placebo arms was seen as early as week 4 and continued through to week 12.

Overall, the data in this submission supports the efficacy of APR 30mg twice daily in the treatment of established active PsA in adult patients from a clinical perspective (i.e. in beneficially treating the symptoms and signs, as well as improving physical functioning) in those with moderately to severely active disease at baseline, with or without concurrent DMARD and/or NSAID. There were numerical and statistically significant improvements with APR versus PBO in terms of clinical response, physical function and some aspects of health related QOL. However, the magnitude of the treatment effect size with APR was modest and smaller than reported for other targeted DMARD therapies, including anti-TNF drugs. Of the 2 APR doses examined in the Phase III PsA program, the 30mg twice daily regimen (versus the 20mg twice daily posology) produced higher numerical responses in most settings.

7.2. Indication 2

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

7.2.1. Pivotal efficacy studies

7.2.1.1. Studies PSOR-008 and PSOR-009

7.2.1.1.1. Study design, objectives, locations and dates

The 2 pivotal Phase III studies of APR monotherapy in PSOR (Studies PSOR-008 and PSOR-009) had a similar study design. Both studies consisted of 4 treatment phases: 1) 16-week, randomized, double-blind, PBO-controlled phase (weeks 0 - 16); 2) 16-week, double-blind maintenance phase (weeks 16 - 32); 3) 20-week randomized, double-blind treatment withdrawal phase (weeks 32 - 52); and 4) additional 4-year, open-label safety extension phase. Subjects could be screened for protocol eligibility for up to 35 days before the baseline visit. The submission contained study reports for the initial 52 weeks of treatment follow-up. The long-term extension phases in both studies are ongoing.

For both studies, eligible subjects at baseline were randomized 2:1 to receive APR 30mg twice daily or PBO during the initial 16-week, PBO-controlled Phase. At week 16, all subjects originally assigned to PBO were transitioned in a blinded fashion to receive APR 30mg twice daily (dose-titrated over the first 6 days of active treatment), while subjects originally assigned to APR 30mg group continued to receive APR 30mg twice daily in a blinded fashion up to week 32 (Maintenance Phase).

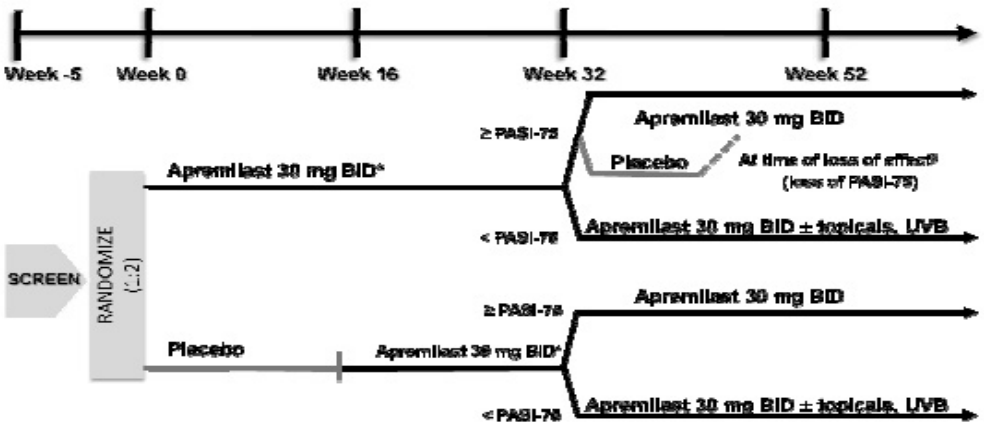
In study PSOR-008 at week 32 (Randomized Treatment Withdrawal Phase), subjects originally randomized to APR at baseline who had achieved a PASI 75 response were re-randomized to

either APR 30mg twice daily or PBO to evaluate time to loss of PASI 75 response. Subjects who were re-randomized to PBO and lost their PASI 75 response re-started APR 30mg twice daily without re-titration. In contrast to Study PSOR-008, Study PSOR-009 utilized a different threshold of PASI response and loss of effect in the Randomized Treatment Withdrawal Phase. At week 32 in Study PSOR-009 (i.e. the start of the Randomized Treatment Withdrawal Phase), subjects originally randomized to APR at baseline who had achieved a PASI 50 response were re-randomized to either APR 30mg twice daily or PBO to evaluate time to loss of 50% of the PASI improvement at week 32 compared to baseline. Subjects who were re-randomized to PBO and lost 50% of their PASI response at week 32 re-started APR 30mg twice daily without re-titration.

In both studies, subjects who were not re-randomized in the Randomized Treatment Withdrawal Phase included subjects who had been randomized to APR at baseline and who did not achieve a PASI 75 response in Study PSOR-008 or a PASI 50 response in Study PSOR-009; and all subjects who had been randomized to PBO at baseline regardless of their PASI response. Subjects who were not re-randomized continued to receive APR 30mg twice daily up to week 52. In addition, those who did not achieve a PASI-75 response in Study PSOR-008 or PASI-50 response in Study PSOR-009 at week 32 were given the option of adding topical and/or ultraviolet B light (UVB) phototherapy to APR treatment. This decision was based on investigator discretion at week 32 only, but therapy could be initiated at any time between weeks 32 and 52. At week 52, all subjects who elected to continue into the long-term extension phases of both studies were treated with APR 30mg twice daily regardless of their response status. Efficacy assessments were done at baseline and weeks 2, 4, 8, 12 and 16 in the PBO-controlled phase; and every 4 weeks (commencing at week 20) during the Maintenance and Randomized Treatment Withdrawal phases.

The trial schema for Study PSOR-008 is presented in Figure 2. Study PSOR-009 had an identical study design schema except that a PASI 50 response at week 32 was the threshold for response/loss of effect, which determined the allocated treatment approach for weeks 32 - 52.

Figure 2: Study Schema for Studies PSOR-008



BID = twice daily; PASI = Psoriasis Area and Severity Index; UVB = ultraviolet B light.
* Doses of apremilast were titrated during the first week 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 at Week 32, 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.

The primary objective of the Phase III PSOR studies was to demonstrate the efficacy of APR (30mg twice daily) in subjects with moderate to severe plaque PSOR at 16 weeks. The major secondary efficacy objectives of the study program included the assessment of the effects of APR upon health related QOL and clinical disease activity (at 16, 32 and 52 weeks of treatment follow-up).

Both of the Phase III PSOR studies were conducted at multiple sites in several countries in Europe, North America (USA and Canada) and Australia. The Phase III PSOR study program was conducted between September 2010 and November 2011. There were 4 amendments to the original protocol in both studies. The first amendment was instituted before the commencement of patient enrolment, and all of the other amendments occurred after. The amendments contained clarifications about baseline assessments, efficacy measures and minor safety related issues. None of the amendments had the potential to have impacted on the integrity of the results.

7.2.1.1.2. Inclusion and exclusion criteria

To be eligible for inclusion in either study, subjects had to be at least 18 years of age with a diagnosis of chronic plaque PSOR for at least 12 months prior to screening. The PSOR had to be moderately to severely active at baseline and screening as defined by having at least 10% BSA involvement, PASI score ≥ 12 and a static Physician Global Assessment (sPGA) score ≥ 3. Eligible subjects were also required to be candidates for systemic or phototherapy.

Co-morbid conditions were an exclusion criterion based on investigator decision as to their clinical significance (including cardiac, pulmonary, neurologic, psychiatric and any major uncontrolled disease). A past history of substance abuse within the last 6 months, infections requiring treatment within 4 weeks of screening, and a history of prolonged sun or UV light exposure were to be excluded. A history of malignancy (except for excised basal or squamous cell skin cancers, or cervical carcinoma in situ successfully treated by surgery) was also an exclusion criterion.

Subjects were screened for Hepatitis B and C, as well as HIV infection at baseline, but not routinely tested for TB apart from requiring a chest X-ray to have been taken within 12 weeks prior to screening. Subjects with active TB or a history of incompletely treated TB were excluded. Subjects with significant laboratory abnormalities at screening and baseline were excluded. This included serum transaminases > 1.5 x ULN, total serum bilirubin > ULN, serum albumin < LLN, serum creatinine > 1.5 mg/dL, total white blood cell count < 3.0 x 109/L or > 14.0 x 109/L, platelet count < 100 x 109/L, haemoglobin < 9.0 g/dL and haemoglobin A1c > 9.0%. Clinically significant abnormalities on 12 lead ECG at screening was also an exclusion criterion.

The eligibility criteria for Studies PSOR-008 and PSOR-009 required subjects to have ceased the majority of topical therapies within 2 weeks of randomisation, including but not limited to CS, retinoid or vitamin D analogue preparations and tacrolimus/pimecrolimus. Exceptions included low potency topical CS, coal-tar shampoo, salicylic acid preparations and un-medicated skin moisturiser. Subjects were to have ceased systemic therapies at least 4 weeks prior to randomisation, and biological treatment at least 12 - 24 weeks beforehand (depending on agent involved). The use of non-study therapies that may affect efficacy assessments were not allowed during the PBO-controlled and maintenance phases. Low potency topical CS for the face, axillae, and groin were allowed. Coal-tar shampoo and salicylic acid preparations for the scalp and un-mdicated skin moisturiser for body lesions were also permitted.

7.2.1.1.3. Study treatments

Following randomisation in both pivotal Phase III PSOR studies, APR was dose-titrated in 10 mg/day increments over the first week of treatment to limit gastrointestinal AEs (primarily mild to moderate nausea). In accordance with the titration schedule proposed by the sponsor in this submission, subjects in the APR 30mg twice-daily treatment arms reached their target dose on day 6. APR was given twice daily, approximately 12 hours apart, without restriction of food or drink. Dose modifications were not permissible in this trial. Background therapy with low potency topical CS (e.g. Class 6 or 7 in the USA classification, such as hydrocortisone), coal-tar shampoo, salicylic acid scalp preparations and un-medicated moisturiser was allowed during

the study. At week 32, all partial responders (e.g. PASI 50 to PASI 74 in Study PSOR-008) had the option of adding topical therapies and/or phototherapy between weeks 32 and 52.

7.2.1.1.4. Efficacy variables and outcomes

The main efficacy variables in the pivotal PSOR trials were the PASI (described earlier in this report) and the static Physician Global Assessment (sPGA). The sPGA is an assessment by the investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from 0 (clear) to 4 (severe), incorporating an assessment of the severity of the 3 primary signs of PSOR: erythema, scaling and plaque elevation. When making the assessment of overall severity, the investigator is instructed to factor in areas that had already been cleared (i.e. have scores of 0) and not just to evaluate remaining lesions for severity (i.e. the severity of each sign was to be averaged across all areas of involvement, including cleared lesions). In the event of different severities across disease signs, the sign that is the predominant feature of the disease was to be used to help determine the sPGA score.

The primary efficacy outcome in both Study PSOR-008 and PSOR-009 was the proportion of subjects treated with APR or PBO who achieved a PASI 75 response at week 16. The major secondary efficacy outcome in both trials was the proportion of subjects in each treatment arm with sPGA of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline to week 16.

Other secondary endpoints included:

- Percentage change from baseline to week 16 in %BSA affected by PSOR and PASI score,
- Proportion of subjects in each treatment group who achieved sPGA score of 0 or 1, as well as other levels of PASI response at week 16,
- Mean change from baseline to week 16 in pruritus VAS, nail disease (as measured by the NAPSI score) and scalp involvement (as assessed by the scPGA),
- Mean change from baseline in health related QOL measures such as the DLQI and SF-36 MCS scores at week 16, and
- Time to loss of PASI response during the Randomized Treatment Withdrawal phase.

The Nail Psoriasis Severity Index (NAPSI) assessed 1 target thumbnail or fingernail representing the worst nail PSOR involvement at baseline. It measures the cosmetic and/or functional impact of nail PSOR. The NAPSI has a range of 0-8 and is the sum of the nail matric score (0 - 4) and the nail bed score (0 - 4). Higher scores indicate greater nail PSOR severity. The scalp Physician Global Assessment (scPGA) is a 6-point scale assessing scalp PSOR involvement. The grading criteria for the scPGA are 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe) and 5 (very severe). Subjects was also asked to assess itch (pruritus) in the previous week by placing a vertical stroke on a 100 mm Visual Analogue Scale (VAS) with 0 = no itch and 100 = worst imaginable itch.

7.2.1.1.5. Randomisation and blinding methods

In both pivotal PSOR studies, subjects were randomized at baseline using a centralised IVRS (Interactive Voice Response System) with no stratification factors. At week 16, subjects randomized to PBO at week 0 were switched to APR 30mg twice daily. At week 32, in order to evaluate the durability of response, relapse, rebound and time to relapse (loss of effect), subjects who were originally randomized to APR and who achieved a PASI 75 response, were re-randomized to either PBO or ongoing APR.

Blinding was maintained until all subjects completed their week 52 assessments in both studies by the use of identical blister cards and identical appearing PBO tablets (matching the APR 10mg, 20mg and 30mg tablets).

7.2.1.1.6. Analysis populations

The primary efficacy analyses were conducted using the FAS population, which consisted of all subjects who were randomized as specified in the protocol. Subjects who were randomized in error and did not receive study medication were excluded from the FAS. The PP cohort was used to support the primary efficacy analysis and consisted of all subjects who had at least 1 post-baseline PASI evaluation and no protocol violations.

7.2.1.1.7. Sample size

The proposed sample size in the Phase III PSOR clinical trial program was to provide a sufficient safety database. In Study PSOR-008, approximately 825 subjects were scheduled to be randomized, with 550 subjects in APR arm and 275 subjects in PBO group. In Study PSOR-009, approximately 405 subjects were scheduled to be randomized, with 270 subjects in APR arm and 135 subjects in PBO group. After week 16, all subjects in both Phase III trials were to be treated with APR until week 32. If the serious adverse event frequency was ≥ 0.2% with APR, the chance to observe at least 1 SAE in 825 subjects was above 80%, and with 405 subjects was > 85%.

Sample size calculations for both of the pivotal Phase III PSOR trials were based on the results of the Phase II study (PSOR-005). In both Phase III studies, a 2-group chi-square test with a 0.05 2-sided significance level would provide 90% power to detect an absolute treatment related difference of 20% (30% versus 10%) between APR and PBO for the proportion of subjects achieving PASI 75 response at week 16, when the total sample size was 189 with a 2:1 randomisation.

7.2.1.1.8. Statistical methods

The primary efficacy endpoint in both studies (PASI 50 or PASI 75 response) was evaluated using both the FAS (primary analysis) and PP (supporting analysis) populations. The proportions of responders in each treatment group achieving the endpoint were analysed using a 2-sided chi-square test at the 0.05 level. Missing values at week 16 were to be imputed using the LOCF method. As a sensitivity analysis, NRI was used as an alternative method for handling missing data. The major secondary endpoint of the change from baseline in the sPGA at week 16 was also analysed using a chi-square test at the 0.05 level, and was conditional on observing a statistically significant result for the primary endpoint comparison. The other 8 secondary efficacy endpoints were to be compared in a hierarchical order of testing using the chi-square test for discrete variables, ANCOVA for continuous variables and the log rank test for time-to-event variables.

7.2.1.1.9. Participant flow

7.2.1.1.9.1. PSOR-008

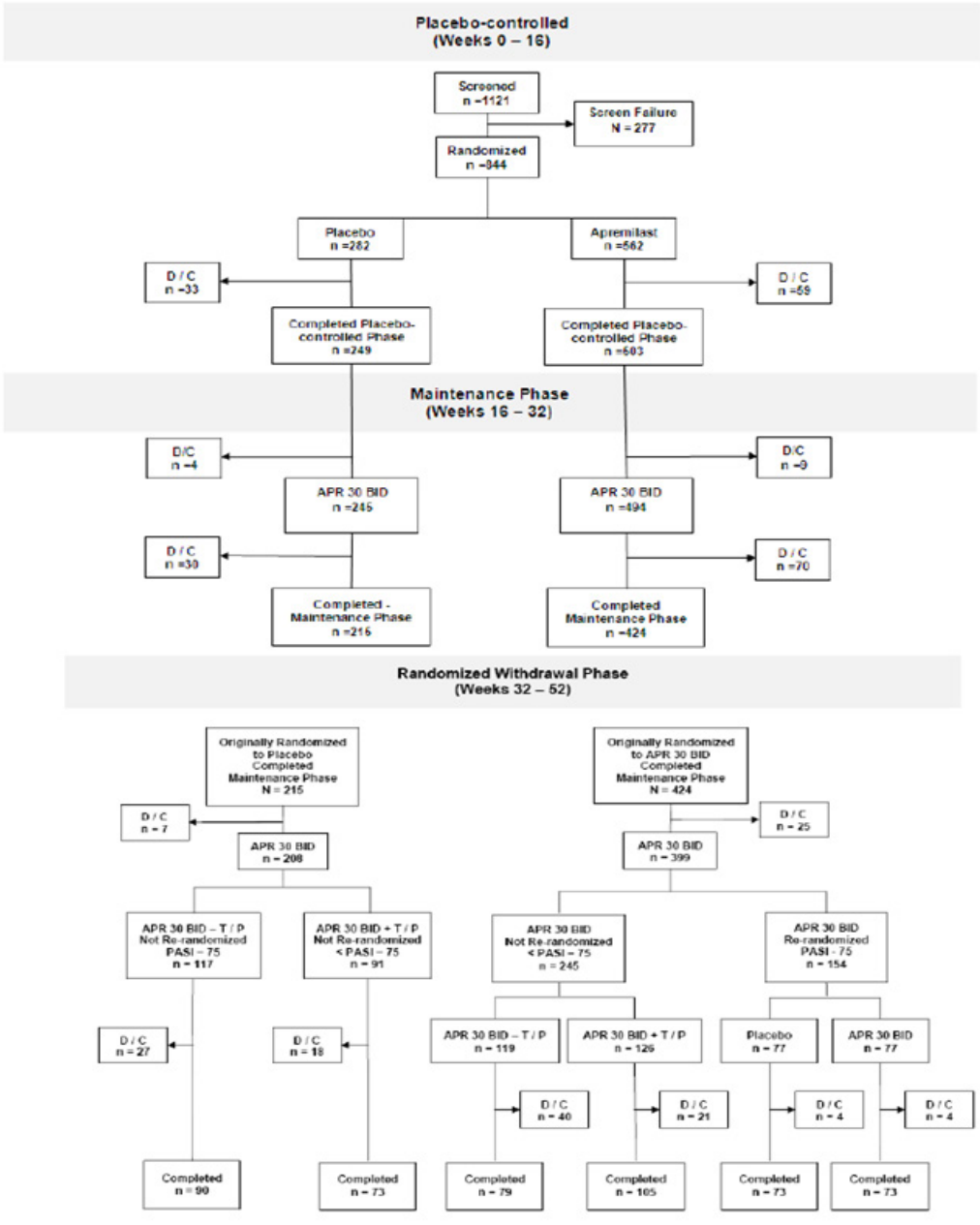
In Study PSOR-008, a total of 1121 subjects were screened for inclusion, of which 844 (562 in the APR treatment group and 282 in the PBO arm) were randomised and included in the FAS at 72 study sites. The most frequent reasons for screen failure (24.7% in total; 277/1121) were failure to meet protocol requirements (6.2%; 69/1121), not meeting safety blood test requirements (5.1%; 57/1121), and insufficient PSOR severity at baseline (5.1%; 57/1121).

A total of 89.1% (752/844) of subjects continued until week 16 at a similar frequency in each of the treatment groups: 88.3% (249/282) in the PBO and 89.5% (503/562) in the APR 30mg arm. The most frequent reasons for discontinuation were AEs (3.3%; 28/844) and subject withdrawal (2.5%; 21/844). AEs occurred at higher frequency in the APR group (4.1% versus 1.8%) and discontinuation due to lack of efficacy was more common in the PBO (2.5% versus 0.4%).

Overall, 87.6% (739/844) of subjects entered the treatment maintenance period (weeks 16 - 32): 86.9% (245/282) in the PBO group and 87.9% (494/562) in the APR 30mg group. Two

patients (1 in each group) did not receive any study medication in the maintenance phase. The percentage of patients who discontinued in the maintenance period was slightly lower in the PBO/APR switch group (12.2%; 30/245) than in the continued APR treatment group (14.2%; 70/494) (Figure 3). Lack of efficacy (7.0%; 52/739), AEs (2.3%; 17/739) and withdrawal of consent (2.0%; 15/739) were the most common reasons for study cessation between weeks 16 and 32.

Figure 3: 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.

7.2.1.1.9.2. PSOR-009

A total of 607 subjects (82.1% of 739) entered the Randomized Treatment Withdrawal period, including 154 subjects who were re-randomized (PASI 75 responders originally randomized to APR at baseline) and 453 subjects who were not re-randomised. Of the 154 re-randomised patients, 146 completed the Randomized Treatment Withdrawal phase, and 140 continued beyond week 52 into the long-term extension period (Figure 3). Lack of efficacy and lost to

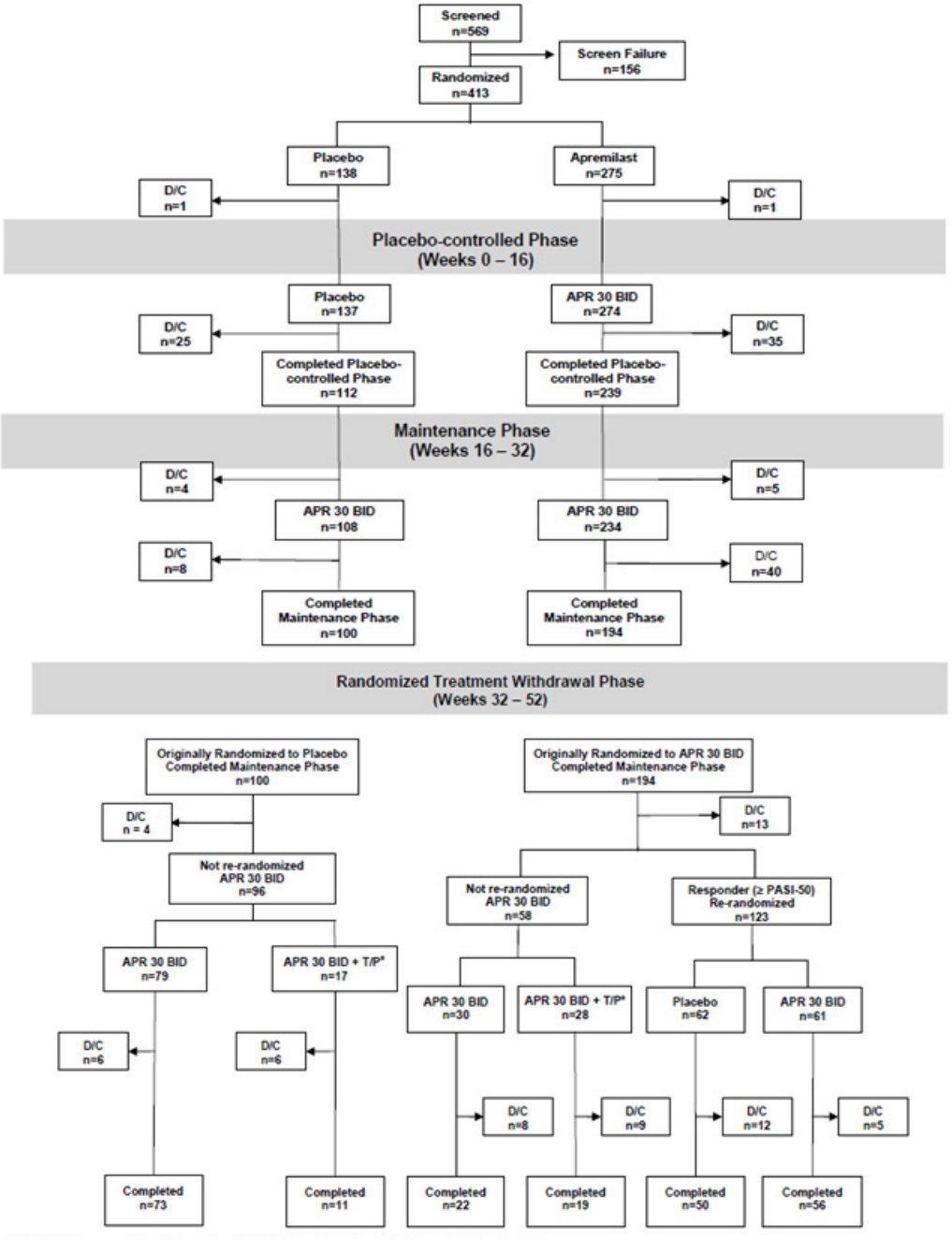
follow-up were the most common reasons for study discontinuation in the Randomized Treatment Withdrawal phase.

In Study PSOR-009, a total of 569 subjects were screened for inclusion at 45 sites, of which 413 (562 in the APR treatment group and 138 in the PBO arm) were randomised. The most frequent reasons for screen failure (27.4% in total; 156/569) were not meeting safety blood test requirements (7.9%; 45/569), insufficient PSOR severity at baseline (6.2%; 35/569) and failure to meet protocol requirements (4.6%; 26/569). One patient in each treatment group was randomised in error, did not receive study medication and therefore was excluded from the FAS. Another 3 subjects (2 in the APR arm and 1 in the PBO group) were correctly randomised but did not receive any study medication. They were still included in the FAS.

A total of 85.0% (351/413) of subjects continued until week 16 at a similar frequency in each of the treatment groups: 81.2% (112/138) in the PBO and 86.9% (239/275) in the APR 30mg arm. The most frequent reasons for discontinuation were AEs (4.8%; 20/413) and subject withdrawal (3.9%; 16/413). All reasons for discontinuation (including AEs, subject withdrawal and lack of efficacy) occurred at similar frequency in both treatment groups.

Overall, 82.8% (342/413) of subjects entered the treatment maintenance period (weeks 16 - 32): 78.3% (108/138) in the PBO group and 85.1% (234/275) in the APR 30mg group. The percentage of patients who discontinued in the maintenance period was lower in the PBO/APR switch group (7.4%; 8/108) than in the continued APR treatment group (17.1%; 40/234) (Figure 4). Lack of efficacy (6.4%; 22/342), AEs (2.9%; 10/342) and withdrawal of consent (2.3%; 8/342) were the most common reasons for study cessation between weeks 16 and 32.

Figure 4: 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.

A total of 277 subjects (81.0% of 342) entered the Randomized Treatment Withdrawal period, including 123 subjects who were re-randomized (PASI 50 responders originally randomized to APR at baseline) and 154 subjects who were not re-randomised. Of the 123 re-randomised patients, 106 (86.2%) completed the Randomized Treatment Withdrawal phase, and 101 continued beyond week 52 into the long-term extension period (Figure 4). Subject withdrawal (4.9%; 6/123) and lack of efficacy (3.3%; 4/123) were the most common reasons for study discontinuation in the Randomized Treatment Withdrawal phase.

7.2.1.1.10. Major protocol violations/deviations

7.2.1.1.10.1. PSOR-008

During the first 52 weeks of the study, a total of 13 subjects (1.5% of 844) were excluded from the PP analysis. Of the 13 affected subjects, 8 received prohibited concomitant medications and/or failed to meet the eligibility criteria, and 5 subjects had missing post-baseline data for the PASI and sPGA evaluations. Major protocol violations occurred at a similar frequency between the 2 treatment groups, and study phases (weeks 0 - 16 and weeks 16 - 32; but none between weeks 32 - 52).

7.2.1.1.10.2. PSOR-009

During the first 52 weeks of the study, a total of 13 subjects (3.1% of 411) were excluded from the PP analysis. Of the 13 affected subjects, 5 failed to meet the eligibility criteria, 2 had study medication dosing errors, 1 received prohibited concomitant medication, and 5 subjects had missing post-baseline data for the PASI and sPGA evaluations. Major protocol violations occurred at a similar frequency between the 2 treatment groups, and study phases (weeks 0 - 16 and weeks 16 - 32; but none between weeks 32 - 52).

7.2.1.1.11. Baseline data

7.2.1.1.11.1. PSOR-008

The demographic characteristics of subjects at baseline were similar across the 2 treatment groups, and were representative of a typical PSOR population in clinical trials. In Study PSOR-008, the majority of subjects were Caucasian (89.7%; 757/844) and male (67.9%; 573/844) with a mean and median age of 46.0 years (range: 18 - 82 years). Mean weight and mean BMI were comparable across the 2 treatment groups at 93.4 kg and 31.3 kg/m2, respectively. Approximately one-half of all subjects were obese (≥ 30 kg/m2) and one-quarter were morbidly obese (≥ 35 kg/m2). Approximately one-third of subjects in Study PSOR-008 were enrolled from USA sites (34.8%; 294/844), just over one-third from Canadian sites (37.6%; 317/844), and approximately 14% each were from sites in Europe (13.9%; 117/844) and Australia (13.7%; 116/844).

The treatment groups were also similar with respect to baseline PSOR features. The mean duration of PSOR for all subjects was 19.4 years (median 16.95 years, range: 1.1 - 70.7 years). The majority of patients had scalp (95.9%; 809/844) and nail disease (68.5%; 578/844). Baseline PSOR characteristics were consistent with moderate to severe disease. The median PASI score was 16.8 (mean 18.95) and the median affected BSA involvement at baseline was 20.0% (mean 24.7%). Almost half of all subjects (49.2%; 415/844) had > 20% BSA involvement at entry, and 29.0% (245/844) had severe disease as measured by PASI score > 20 or sPGA of 4 or greater.

The PSOR-related therapies that were used by subjects prior to enrolment were generally well balanced across the 2 treatment groups. The majority of patients (95.0%) had received treatment with at least 1 therapy, of which dermatological agents (89.0%) such as topical CS was the most common. Approximately two-thirds of all subjects (64.8%; 547/844) had been treated previously with either systemic therapy (most frequently MTX or CsA) and/or phototherapy. Conversely, more than one-third of all subjects (35.2%; 297/844) in Study PSOR-008 were naïve to prior systemic and/or phototherapy, which is relevant to the sponsor requested treatment indication. In addition, 28.7% (242/844) of subjects had prior exposure to biologics (6.6% [56/844] with documented treatment failures), including 17.7% (149/844) with previous anti-TNF experience.

The incidence of relevant co-morbid conditions was similar in the treatment groups. A past history of hypertension was recorded in 30.7% of all subjects (259/844), 13.7% (116/844) reported hyperlipidaemia and 9.7% (82/844) had type 2 diabetes mellitus. Past history of depression was recorded in 13.9% of patients (117/844). Five subjects had a risk of developing

TB, including latent TB (3 subjects), past pulmonary TB (1 subject) and positive tuberculin skin test (1 subject). More than two-thirds of all subjects (69.4%; 586/844) were current alcohol drinkers and 34.8% (294/844) were current tobacco users.

7.2.1.1.11.2. PSOR-009

The demographic characteristics of subjects at baseline were similar across the 2 treatment groups. In Study PSOR-009, the majority of subjects were Caucasian (92.0%; 378/411) and male (67.2%; 276/411) with a mean and median age of 46.0 years (range: 18 - 83 years). Mean weight and mean BMI were comparable across the 2 treatment groups at 91.1 kg and 30.8 kg/m2, respectively. Half of all subjects were obese (≥ 30 kg/m2) and one-quarter were morbidly obese (≥ 35 kg/m2). Regarding site of enrolment, approximately one-half of all subjects in Study PSOR-009 were enrolled from the USA (50.1%; 206/411) followed by 27.5% (113/411) from sites in Europe and 22.4% (92/411) from Canadian centres.

The treatment groups were also similar with respect to baseline PSOR features. The mean duration of PSOR for all subjects was 18.2 years (median 15.8 years, range: 0.9 - 51.9 years). The majority of patients had scalp (92.7%; 381/411) and nail disease (67.6%; 278/411). Baseline PSOR characteristics were consistent with moderate to severe disease. The median PASI score was 16.8 (mean 19.3) and the median affected BSA involvement at baseline was 21.5% (mean 26.2%). Over half of all subjects (54.3%; 223/411) had > 20% BSA involvement at entry, and 35.8% (147/411) had severe disease as measured by PASI score > 20 or sPGA of 4 or greater.

The PSOR-related therapies that were used by subjects prior to enrolment were generally well balanced across the 2 treatment groups. The majority of patients (92.9%) had received treatment with at least 1 therapy, of which dermatological agents (85.4%) such as topical CS was the most common. Approximately two-thirds of all subjects (64.2%; 264/411) had been treated previously with either systemic therapy (most frequently MTX or CsA) and/or phototherapy. In addition, 33.1% (136/411) of subjects had prior exposure to biologics (8.5% [35/411] with documented treatment failures), including 24.8% (102/411) with previous anti-TNF experience.

The incidence of relevant co-morbid conditions was similar in the treatment groups. A past history of hypertension was recorded in 32.8% of all subjects (135/411), 21.4% (88/411) reported hyperlipidaemia and 10.5% (43/411) had type 2 diabetes mellitus. Past history of depression was recorded in 13.1% of patients (54/411). Four subjects (3 received APR) had a risk of developing TB, including past TB (2 subjects), latent TB (1 subject) and positive tuberculin skin test (1 subject). The majority of subjects (62.8%; 258/411) were current alcohol drinkers and 39.4% (162/411) were current tobacco users.

7.2.1.1.12. Results for the primary efficacy outcome

7.2.1.1.12.1. PSOR-008

The primary endpoint of Study PSOR-008 was met as a statistically significant greater proportion of subjects treated with APR 30mg twice daily achieved a PASI 75 response at week 16 (33.1%; 186/562) compared with PBO-treated subjects (5.3%; 15/282). The treatment related difference was 27.8 (95% CI 23.1, 32.5; $p < 0.0001$). The results of the primary analysis were supported by the sensitivity analyses conducted to assess the impact of missing data. Sensitivity analyses included using NRI as alternative method to LOCF for handling missing data, as well as examining the PP population versus FAS. Using the NRI, a significantly greater proportion of subjects in the APR treatment group (32.6%; 183/562) achieved PASI 75 response at week 16 compared to PBO (5.0% [14/282]; $p < 0.001$). The PP cohort using LOCF showed a statistically greater proportion of PASI 75 responders in the APR (33.3%; 185/555) versus PBO (5.4% [15/276]; $p < 0.001$).

Subgroup analyses across multiple demographic and disease characteristics were performed for the rate of PASI 75 response at week 16. There was no association between baseline PSOR

severity (moderate versus severe) and better response following APR. Similarly, subject BMI at baseline and prior treatment with systemic (including biologic) therapies did not predict treatment response. There was a trend towards slightly higher PASI 75 response in female patients, those who resided outside the USA and current non-smokers. The clinical significance of these observations is unclear.

7.2.1.1.12.2. PSOR-009

A statistically greater proportion of subjects treated with APR 30mg twice daily achieved a PASI 75 response at week 16 (28.8%; 79/274) compared with PBO-treated subjects (5.8%; 8/137). The treatment related difference was 23.0 (95% CI 16.3, 29.6; $p < 0.0001$). The results of the primary analysis were supported by the sensitivity analyses conducted to assess the impact of missing data. Sensitivity analyses included using NRI as alternative method to LOCF for handling missing data, as well as examining the PP population versus FAS. Using the NRI, a significantly greater proportion of subjects in the APR treatment group (28.1%; 77/274) achieved PASI 75 response at week 16 compared to PBO (5.1% [7/137]; $p < 0.001$). The PP cohort using LOCF showed a statistically greater proportion of PASI 75 responders in the APR (29.7%; 79/266) versus PBO (6.0% [8/134]; $p < 0.001$).

Subgroup analyses across multiple demographic and disease characteristics were performed for the rate of PASI 75 response at week 16. There was no association between baseline PSOR severity (moderate versus severe) and better response following APR. Similarly, subject BMI at baseline and prior treatment with systemic (including biologic) therapies did not predict treatment response.

7.2.1.1.13. Results for other efficacy outcomes

7.2.1.1.13.1. PSOR-008

A statistically significant greater proportion of subjects treated with APR 30mg twice daily achieved the major secondary efficacy outcome (i.e. improvement of sPGA score to 0 - 1 with at least a 2-point reduction from baseline) at week 16 compared with PBO-treated subjects (21.7% [122/562] for APR versus 3.9% [11/282]). The treatment related difference was 17.8 (95% CI 13.7, 21.9; $p < 0.0001$). The results of the primary analysis for this endpoint were supported by the sensitivity analyses using the NRI (versus LOCF method) for handling missing data as well as the PP population (versus FAS).

Statistically significant improvements were seen with APR compared to PBO across the majority of the other secondary efficacy endpoints including percentage affected BSA involvement, mean PASI scores, PASI 50 response, pruritus VAS, DLQI and SF-36 MCS score at week 16. In addition, statistically meaningful improvements in difficult to treat areas commonly affected by PSOR, such as the nails (mean NAPSI) and scalp (as measured by changes in the ScPGA) were also observed. At 16 weeks, the mean percentage reduction from baseline in BSA involvement for the PBO group was -6.9% (%BSA involvement went from 25.0% to 23.2%) compared with -47.8% (%BSA involvement went from 24.4% to 13.2%) for APR ($p < 0.0001$). The mean percentage reduction from baseline in PASI score at week 16 for the PBO group was -16.7% (mean PASI score went from 19.32 to 16.23) compared with -52.1% (mean PASI score went from 18.73 to 9.08) for APR ($p < 0.0001$). At week 16, a statistically significant greater proportion of subjects treated with APR (58.7%; 330/562) achieved a PASI 50 response compared to 17.0% (48/282) in the PBO arm ($p < 0.0001$). Subjects treated with APR recorded a 31.5mm mean reduction in pruritus VAS over 16 weeks (from 66.2mm to 34.7mm). In the PBO group, the mean pruritus VAS reduced by 7.3mm (from 65.2mm to 57.9mm). The treatment difference for the mean change in pruritus VAS was also statistically significant ($p < 0.0001$). The mean DLQI scores at baseline were 12.1 and 12.7 for subjects randomized to PBO and APR, respectively. Subjects treated with APR achieved a statistically significant reduction in the DLQI score at week 16 (-6.6) compared with PBO (-2.1; $p < 0.0001$). The mean SF-36 MCS scores at baseline were 47.0 and 45.8 for subjects randomized to PBO and APR, respectively. Subjects

treated with APR achieved a nominally significant improvement (increase) in the SF-36 MCS score at week 16 (2.4) compared with PBO (-1.0; $p < 0.0001$).

The mean NAPSI scores at baseline were 4.4 and 4.3 for subjects randomized to PBO (n = 178 of 195) and APR (n =339 of 363), respectively. Subjects treated with APR achieved a nominally significant mean percentage reduction in the NAPSI score at week 16 (-22.5%) compared with PBO (6.5%; $p < 0.0001$). Among subjects with moderate to severe scalp PSOR at baseline, a significantly greater proportion of patients treated with APR (46.5%; 174/374) achieved a scPGA score of 0 or 1 at week 16 compared to PBO (17.5% [33/189]; nominal $p < 0.0001$).

Various levels of PASI response (50/70/90) over time between weeks 0 and 32 was an exploratory analysis in Study PSOR-008. Differential response to APR treatment compared with PBO was demonstrated as early as week 4. The maximal rate of PASI 75 and sPGA responses were observed at week 16 and week 24, respectively, and responses were generally maintained up to week 32.

Time to first loss of PASI 75 response (i.e. loss of treatment effect) was an important secondary endpoint in the PSOR-008 Study, which is relevant to the regulatory guideline as well. Maintenance of response was better with continuous APR treatment (n = 77) compared to treatment withdrawal (n = 77). The PASI 75 responders who were re-randomized to PBO at week 32 (Randomized Treatment Withdrawal Phase) lost their PASI 75 response significantly faster than subjects re-randomized to APR. The median time to first loss of PASI 75 response was 5.1 weeks for PBO (n = 64 of 77) and 17.7 weeks for APR 30mg twice daily (n = 40 of 77; nominal $p < 0.0001$). At week 52, 58.4% (45/77) of subjects re-randomized to APR treatment at week 32 were PASI 75 responders compared with 11.7% (9/77) re-randomized to PBO at week 32 who then remained on PBO through to week 52. Furthermore, of the subjects who were re-randomized to APR at week 32, 87.0% (67/77) had at least a PASI 50 response and 24.7% (19/77) had a PASI 90 response at week 52. Of the subjects re-randomized to PBO at week 32, 83.1% (64/77) lost their PASI 75 response during the Randomized Treatment Withdrawal Phase and were re-started on APR before week 52. The majority (70.3%; 45/64) of these subjects regained PASI 75 response following re-initiation of APR, with 51.6% (33/64) of subjects regaining PASI 75 response within 4 weeks after APR re-treatment.

Subjects who were originally randomized to PBO, treated with APR between weeks 16 - 32, and who were not PASI 75 responders at week 32 (n = 135) also tended to maintain a clinically meaningful (> PASI 50 response) and a stable mean percentage change in PASI score through to week 52. In addition, subjects in this cohort who were not PASI 75 responders at week 32 but who then added topical and/or phototherapy to APR at weeks 32 - 52 achieved a greater mean percentage decrease in PASI score at week 52 (-61.3%) compared with those subjects treated with no topical treatment in weeks 32 - 52 (-52.6%).

7.2.1.1.13.2. PSOR-009

A statistically significant greater proportion of subjects treated with APR 30mg twice daily achieved the major secondary efficacy outcome (i.e. improvement of sPGA score to 0 - 1 with at least a 2-point reduction from baseline) at week 16 compared with PBO-treated subjects (20.4% [56/274] for APR versus 4.4% [6/137]). The treatment related difference was 16.1 (95% CI 10.2, 21.9; $p < 0.0001$). The results of the primary analysis for this endpoint were supported by the sensitivity analyses using the NRI (versus LOCF method) for handling missing data as well as the PP population (versus FAS).

Statistically significant improvements were seen with APR compared to PBO across the majority of the other secondary efficacy endpoints including percentage affected BSA involvement, mean PASI scores, PASI 50 response, pruritus VAS, DLQI and SF-36 MCS score at week 16. In addition, statistically meaningful improvements in difficult to treat areas commonly affected by PSOR, such as the nails (mean NAPSI) and scalp (as measured by changes in the ScPGA) were also observed. At 16 weeks, the mean percentage reduction from baseline in BSA involvement for

the PBO group was -6.14% (%BSA involvement went from 27.64% to 26.15%) compared with -48.45% (%BSA involvement went from 25.53% to 13.33%) for APR ($p < 0.0001$). The mean percentage reduction from baseline in PASI score at week 16 for the PBO group was -15.8% (mean PASI score went from 20.09 to 17.15) compared with -50.9% (mean PASI score went from 18.99 to 9.42) for APR ($p < 0.0001$). At week 16, a statistically significant greater proportion of subjects treated with APR (55.5%; 152/274) achieved a PASI 50 response compared to 19.7% (27/137) in the PBO arm ($p < 0.0001$). Subjects treated with APR recorded a 33.5mm mean reduction in pruritus VAS over 16 weeks (from 67.8mm to 34.3mm). In the PBO group, the mean pruritus VAS reduced by 12.2mm (from 65.0mm to 52.8mm). The treatment difference for the mean change in pruritus VAS was also statistically significant ($p < 0.0001$). The mean DLQI scores at baseline were 12.8 and 12.5 for subjects randomized to PBO and APR, respectively. Subjects treated with APR achieved a statistically significant reduction in the DLQI score at week 16 (-6.7) compared with PBO (-2.8; $p < 0.0001$). The mean SF-36 MCS scores at baseline were 45.3 and 45.4 for subjects randomized to PBO and APR, respectively. Subjects treated with APR achieved a nominally significant improvement (increase) in the SF-36 MCS score at week 16 (2.6) compared with PBO (no change; $p < 0.0001$).

The mean NAPSI scores at baseline were 4.4 and 4.2 for subjects randomized to PBO (n = 84 of 91) and APR (n = 163 of 175), respectively. Subjects treated with APR achieved a nominally significant mean percentage reduction in the NAPSI score at week 16 (-29.0%) compared with PBO (-7.1%; $p < 0.0001$). Among subjects with moderate to severe scalp PSOR at baseline, a significantly greater proportion of patients treated with APR (40.9%; 72/176) achieved a scPGA score of 0 or 1 at week 16 compared to PBO (17.2% [16/93]; nominal $p < 0.0001$).

Various levels of PASI response (50/70/90) over time between weeks 0 and 32 was an exploratory analysis in Study PSOR-008. Differential response to APR treatment compared with PBO was demonstrated as early as week 4. The maximal rate of PASI 50 and sPGA responses were observed at week 16, and responses were maintained through to week 32.

Time to first loss of 50% improvement (Kaplan-Meier estimate) was an important secondary endpoint in the PSOR-009 Study. Maintenance of response was better with continuous APR treatment (n = 61) compared to treatment withdrawal (n = 62). The PASI 50 responders who were re-randomized to PBO at week 32 (Randomized Treatment Withdrawal Phase) lost 50% of their improvement at a median time of 12.4 weeks for PBO (n = 35 of 62) compared with 21.9 weeks for continued APR 30mg twice daily (n = 7 of 61; nominal $p < 0.0001$). At week 52, 80.3% (49/61) of subjects re-randomized to APR treatment at week 32 were PASI 50 responders or greater compared with 24.2% (15/62) re-randomized to PBO at week 32 who then remained on PBO through to week 52. Furthermore, of the subjects who were re-randomized to APR at week 32, 49.2% (30/61) had at least a PASI 75 response and 23.0% (14/61) had a PASI 90 response at week 52. Of the subjects re-randomized to PBO at week 32, 51.6% (32/62) lost at least 50% of their PSOR improvement during the Randomized Treatment Withdrawal Phase and were re-started on APR before week 52. The majority (65.6%; 21/32) of these subjects regained PASI 50 response following re-initiation of APR, with 51.7% (15/32) of subjects regaining PASI 50 response within 8 weeks after APR re-treatment.

7.2.1.2. Study PSOR-005

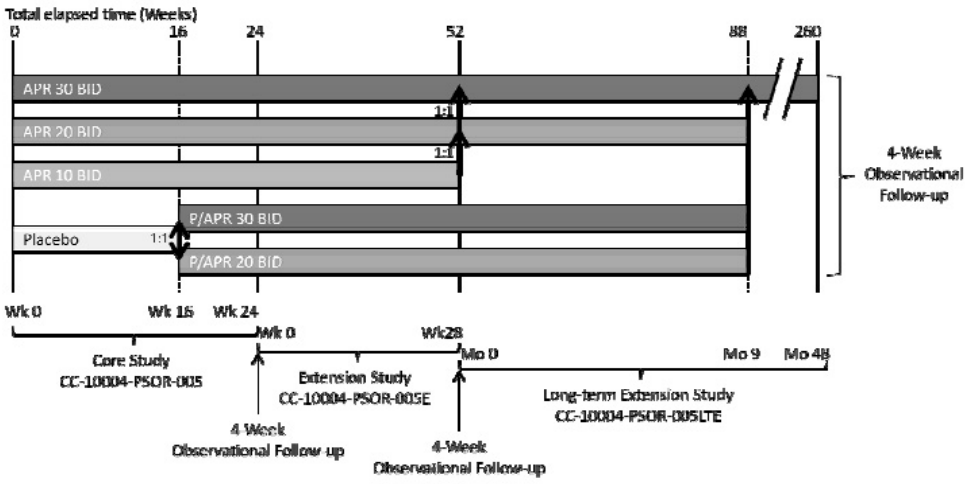
7.2.1.2.1. Study design, objectives, locations and dates

Study PSOR-005 was a Phase IIb, randomized, double-blind, PBO-controlled, dose-ranging trial in 325 subjects with moderate to severe plaque PSOR who were candidates for systemic therapy or phototherapy. At the time of the study initiation, 2 studies had been completed in PSOR – PSOR-001 (proof of concept) and PSOR-003 (Phase II trial examining APR 20mg once daily and 20mg twice daily). Study PSOR-003 suggested that an increase in APR dose to 30mg twice daily with 16 weeks of treatment follow-up would help determine the optimal doses of APR for investigation in the Phase III PSOR program. Study PSOR-005 had 3 periods, which

were conducted as distinct studies under separate protocols. There was 24-week core study, followed by a 28-week extension study phase and then a 4-year long term extension trial. The submission contained data up to month 9 (week 88) of the long-term extension study (i.e. 21 months of exposure to APR). The core study had a pre-randomisation period of up to 4 weeks, a 16-week PBO-controlled treatment phase, an 8-week active treatment phase and a 4-week observational follow-up period. The extension studies included only active treatment phases and a 4-week observational follow-up period.

Subjects meeting eligibility criteria at baseline were randomised 1:1:1:1 to PBO, APR 10mg twice daily, APR 20mg twice daily or APR 30mg twice daily. After 16 weeks, all subjects originally assigned to the PBO group were re-randomised 1:1 to receive APR 20mg twice daily or APR 30mg twice daily. At week 24, subjects who entered the extension phase continued the same treatment that they were receiving at the end of the core study. At week 52, subjects who had received APR 20mg or 30mg twice daily during the first extension period continued the same treatment. Subjects who received APR 10mg twice daily during the first extension period were re-randomised 1:1 to either APR 20mg twice daily or APR 30mg twice daily. Once the final dose of APR for the Phase III program was selected, all subject were to be switched to open-label APR starting at month 6 (or subsequent visit if after 6 months) in the long term extension study. The trial schema for Study PSOR-008 is presented in Figure 5. During the core study, efficacy assessments were performed at weeks 1 and 2, and every 2 weeks thereafter. In the extension study, efficacy assessments were conducted every 4 weeks and in the long term extension trial efficacy evaluations were scheduled every 3 months.

Figure 5: Study Schema for Studies PSOR-005



APR = apremilast; BID = twice daily; Mo = month; P = placebo; Wk = week
At Week 16, subjects originally randomized to placebo were re-randomized 1:1 to receive either APR 20 BID or APR 30 BID.
At Week 52, subjects originally randomized to APR 10 BID were re-randomized 1:1 to receive either APR 20 BID or APR 30 BID.
At Week 88, all subjects transitioned to APR 30 BID
Subjects entered the 4-week observational follow-up either a) once completing the Week 24 or Week 52 visits if they did not enter the next study, or b) after their final visit if they discontinued from the study prematurely, regardless of time point.

The primary objective of the core study was to demonstrate the efficacy of 3 different oral doses of APR (10mg, 20mg and 30mg – all taken twice daily) in subjects with moderate to severe plaque PSOR. The primary objective of the extension studies was to evaluate the maintenance of treatment effect with APR. Health related QOL was also investigated in Study PSOR-005.

Study PSOR-005 was conducted at 20 active sites in the USA and 15 active centres in Canada. The core trial enrolled its first subject in September 2008 and the last patient completed the core study period in July 2011, however, the long term extension phase is ongoing. There core study had 1 protocol amendment, the extension trial also had 1 amendment and the long term extension study had 2 protocol amendments. The amendments contained clarifications about definitions and minor safety related issues. None of the amendments had the potential to have impacted on the integrity of the results.

7.2.1.2.2. Inclusion and exclusion criteria

To be eligible for inclusion, subjects had to be at least 18 years of age with a diagnosis of chronic plaque PSOR for at least 6 months prior to screening. The PSOR had to be moderately to severely active at baseline and screening as defined by having at least 10% BSA involvement and a PASI score ≥ 12. Eligible subjects were also required to be candidates for systemic or phototherapy.

Co-morbid conditions were an exclusion criterion based on investigator decision as to their clinical significance (including cardiac, pulmonary, neurologic, psychiatric and any major uncontrolled disease). A history of malignancy (except for excised basal or squamous cell skin cancers, or cervical carcinoma in situ successfully treated by surgery), as well as pregnancy and lactation were exclusion criterion.

Subjects were screened for Hepatitis B and C, HIV and TB at baseline (using Purified Protein Derivative [PPD] skin test and chest X-ray. Subjects with active TB or a history of incompletely treated TB (within the last 3 years) were excluded. Subjects with significant laboratory abnormalities at screening and baseline were excluded. This included serum transaminases > 1.5 x ULN, total serum bilirubin > 2 mg/dL, serum creatinine > 1.5 mg/dL, total white blood cell count < 3.0 x 109/L or > 14.0 x 109/L, platelet count < 100 x 109/L, and haemoglobin < 9.0 g/dL. Clinically significant changes on 12 lead ECG at screening was also an exclusion criterion.

The eligibility criteria for Study PSOR-005 required subjects to have ceased the majority of topical therapies within 2 weeks of randomisation, including but not limited to CS, retinoid or vitamin D analogue preparations, tacrolimus and anthralin. Exceptions included low potency topical CS, coal-tar shampoo, salicylic acid preparations and un-medicated skin moisturiser. Subjects were to have ceased systemic therapies at least 4 weeks prior to randomisation, and biological treatment at least 12 - 24 weeks beforehand (depending on agent involved). Low potency topical CS for the face, axillae, and groin were allowed. Coal-tar shampoo and salicylic acid preparations for the scalp and un-medicated skin moisturiser for body lesions were also permitted.

7.2.1.2.3. Study treatments

Following randomisation, APR was dose-titrated in 10 mg/day increments over the first week of treatment to limit gastrointestinal AEs (primarily mild to moderate nausea). In accordance with the titration schedule proposed by the sponsor in this submission, subjects in the APR 20mg twice-daily treatment groups reached their target dose on day 4, and subjects in the APR 30mg twice-daily treatment arms reached their target dose on day 6. APR was given twice daily, approximately 12 hours apart, without restriction of food or drink. Dose modifications were not permissible in this trial. Background therapy with low potency topical CS (e.g. Class 6 or 7 in the USA classification, such as hydrocortisone), coal-tar shampoo, salicylic acid scalp preparations and un-medicated moisturiser was allowed during the study.

7.2.1.2.4. Efficacy variables and outcomes

The primary efficacy outcome of Study PSOR-005 was the proportion of subjects in each treatment group who obtained PASI 75 response at week 16. Secondary efficacy outcomes (evaluated at weeks 16, 24 and 52) included the rates of PASI response, LS mean percentage change from baseline in the PASI score, proportion of subjects achieving sPGA score of 0 or 1, LS mean percentage change from baseline in PSOR affected %BSA, and the change from baseline in DLQI and SF-36 scores.

7.2.1.2.5. Randomisation and blinding methods

Subjects were randomized at baseline using a centralised IVRS with no stratification factors. After 16 weeks, all subjects originally assigned to the PBO group were re-randomised 1:1 to receive APR 20mg twice daily or APR 30mg twice daily. At week 24, subjects who entered the extension phase continued the same treatment that they were receiving at the end of the core

study. At week 52, subjects who had received APR 20mg or 30mg twice daily during the first extension period continued the same treatment. Subjects were received APR 10mg twice daily during the first extension period were re-randomised 1:1 to either APR 20mg twice daily or APR 30mg twice daily. Once the final dose of APR for the Phase 3 program was selected, all subject were to be switched to open-label APR starting at month 6 (or subsequent visit if after 6 months) in the long-term extension study. Blinding was maintained by the use of identical blister cards and identical appearing PBO tablets (matching the APR 10mg, 20mg and 30mg tablets).

7.2.1.2.6. Analysis populations

The primary efficacy analysis was conducted using the ITT population, which consisted of all randomized subjects. The PP cohort was used to support the primary efficacy analysis and consisted of all subjects who had at least 1 post-baseline PASI evaluation and no protocol violations.

7.2.1.2.7. Sample size

Based on the available literature and the results of Study PSOR-003, it was estimated that a 25% difference between active (35% response rate) and PBO treatment (10% response rate) may be expected and clinically relevant. A 2-group continuity corrected chi-square test with a 0.05, 2-sided significance level would have 90% power to detect a 25% treatment related difference if the sample size in each group was 65 subjects. However, the study aimed to recruit 87 subjects (348 in total) in each treatment group as the assumed dropout rate was 25%.

7.2.1.2.8. Statistical methods

The primary efficacy endpoint in Study PSOR-005 (PASI 75 response at week 16) was evaluated using both the ITT (primary analysis) and PP (supporting analysis) populations. The proportions of responders in each treatment group achieving the endpoint were analysed using a 2-sided chi-square test at the 0.05 level. Missing values at week 16 were to be imputed using the LOCF method. As a sensitivity analysis, NRI was used as an alternative method for handling missing data. The secondary efficacy endpoints with discrete variables were also analysed using a chi-square test at the 0.05 significance level (ITT population, using LOCF method for missing data). The secondary efficacy endpoints with continuous variables were compared using ANCOVA and the log rank test was used for time-to-event variables such as the time to relapse.

7.2.1.2.9. Participant flow

A total of 542 subjects were screened for involvement in this study, of which 190 (35.1%) were screen failures. The most common reasons for screen failure were: unable to adhere to study visit schedule (n = 37), not meeting safety laboratory criteria (n = 37), not having PSOR for at least 6 months (n = 32), not being of sufficiently good health according to site investigator (n = 27) and positive screening PPD test (n = 26).

A total of 352 subjects (88 in both the PBO and APR 30mg twice daily groups, 87 in the APR 20mg twice daily arm and 89 in the APR 10mg twice daily group) were randomized and received at least 1 dose of study medication. The rates of completion until week 16 (PBO-controlled period for primary efficacy endpoint) were different between the treatment groups: 81.8% (72/88) in the PBO group, 88.8% (79/89) in the APR 10mg twice daily group, 75.9% (66/87) in the APR 20mg arm and 79.5% (70/88) in the APR 30mg group. The most common reason for premature discontinuation before week 16 was AEs, which occurred at a higher incidence in the APR 20mg and 30 mg treatment groups (9.2% [8/87] and 11.4% [10/88], respectively) versus 5.7% (5/88) in the PBO group and 1.1% (1/89) in the APR 10mg arm. In addition, another 7 subjects (2 each in the PBO and APR 10mg groups, and 3 in the APR 30mg arm) completed the week 16 evaluations but did not continue in the trial. At week 16, 70 subjects in the PBO group were re-randomised to APR because of insufficient PASI response (34 to APR 20mg twice daily and 36 to APR 30mg twice daily).

As summarised in Table 14, a total of 280 subjects (77 in the APR 10mg group, 66 in the APR 20mg arm, 67 in the APR 30mg group and 70 re-randomised PBO subjects) were involved between weeks 16 and 24 of the core study period. In all of the treatment groups between weeks 16 and 24, > 84% of continuing subjects completed this treatment phase. The majority of subjects who remained involved in Study PSOR-005 at 24 weeks, entered the first extension phase (74.6%; 209/280) and most of those subjects completed the follow-up period to week 52 (74.6%; 156/209). However, only a small number of patients (n = 33) entered the long-term extension phase (beyond week 52), 28 of which are still continuing at week 88. It remains unclear as to why participating patient numbers decreased significantly after week 52.

Table 14: Subject Disposition in Study PSOR-005 between Weeks 16 and 88

Week 16 – Week 24 (Core Study; Active Treatment Period) N = 280					
	APR 10 BID n (%)	APR 20 BID n (%)	APR 30 BID n (%)	P/APR 20 BID n (%)	P/APR 30 BID n (%)
Entered the period	77	66	67	34	36
Discontinued	12 (15.6)	7 (10.6)	2 (3.0)	1 (2.9)	5 (13.9)
Adverse event	4 (5.2)	0	0	1 (2.9)	2 (5.6)
Lack of efficacy	4 (5.2)	4 (6.1)	1 (1.5)	0	0
Withdrawal by subject	1 (1.3)	1 (1.5)	0	0	2 (5.6)
Lost to follow-up	1 (1.3)	1 (1.5)	0	0	0
Protocol violation	1 (1.3)	1 (1.5)	1 (1.5)	0	1 (2.8)
Other	1 (1.3)	0	0	0	0
Completed the period	65 (84.4)	59 (89.4)	65 (97.0)	33 (97.1)	31 (86.1)
Completed the period and continued to Extension Study	47 (61.0)	50 (75.8)	58 (86.6)	27 (79.4)	27 (75.0)
Week 24 – Week 52 (Extension Study; Active Treatment Period) N = 209					
	APR 10 BID n (%)	APR 20 BID n (%)	APR 30 BID n (%)	P/APR 20 BID n (%)	P/APR 30 BID n (%)
Entered the period	47	50	58	27	27
Discontinued	13 (27.7)	17 (34.0)	10 (17.2)	5 (18.5)	8 (29.6)
Adverse event	0	0	0	2 (7.4)	1 (3.7)
Lack of efficacy	8 (17.0)	10 (20.0)	3 (5.2)	1 (3.7)	2 (7.4)
Withdrawal by subject	3 (6.4)	1 (2.0)	2 (3.4)	2 (7.4)	3 (11.1)
Lost to follow-up	2 (4.3)	5 (10.0)	3 (5.2)	0	1 (3.7)
Other	0	1 (2.0)	2 (3.4)	0	1 (3.7)
Completed the period	34 (72.3)	33 (66.0)	48 (82.8)	22 (81.5)	19 (70.4)
Completed the period and continued to Long-term Extension Study	5 (10.6)	10 (20.0)	10 (17.2)	4 (14.8)	4 (14.8)
Week 52 – Week 88 (Long-term Extension Study; Active Treatment Period) N = 33					
	APR 20 BID n[b]		APR 30 BID n[c]		
Entered the period	16		17		
Discontinued	4		1		
Lack of efficacy	1		0		
Withdrawal by subject	2		1		
Lost to follow-up	1		0		
Completed the period/Ongoing	12		16		

APR = apremilast; BID = twice daily; P = placebo.

[a] This incidence includes two events of pregnancy.

[b] This includes subjects who were randomized to APR 20 BID at Week 0, subjects who were originally randomized to placebo but were re-randomized to APR 20 BID at Week 16, and subjects originally randomized to APR 10 BID and were re-randomized to APR 20 BID at Week 52.

[c] This includes subjects who were randomized to APR 30 BID at Week 0, subjects who were originally randomized to placebo but were re-randomized to APR 30 BID at Week 16, and subjects originally randomized to APR 10 BID and were re-randomized to APR 30 BID at Week 52.

7.2.1.2.10. Major protocol violations/deviations

During the 16-week PBO-controlled phase of Study PSOR-005, a total of 25 subjects (7.1% of 352) had major protocol deviations recorded that may have impacted upon efficacy assessments. Such violations occurred at a higher incidence in the APR 10mg twice-daily group (10.1%; 9/89) compared with the other 3 treatment groups (5.7 - 6.9%; 5 - 6 subjects in each arm). During the first extension period (weeks 24 - 52), 10 subjects had significant protocol violations, which were evenly recorded across the different treatment groups (2.6 - 4.5% incidence).

7.2.1.2.11. Baseline data

The demographic characteristics of subjects at baseline were similar across the 4 treatment groups. In Study PSOR-005, the majority of subjects were Caucasian (92.9%; 327/352) and male (62.8%; 221/352) with a mean age of 44.3 years (range: 18 - 80 years). Less than 10% of all subjects (8.5%; 30/352) were aged 65 years or older. The mean BMI of the enrolled subjects was 31.2 kg/m2 (range: 16.5 - 63.4 kg/m2). The treatment groups were also similar with respect to baseline PSOR features. The mean duration of PSOR for all subjects was 19.0 years, and 21.0% (74/352) of patients had concurrent PsA. The majority of patients had scalp (93.8%; 330/352) and nail disease (59.7%; 210/352). Baseline PSOR characteristics were consistent with moderate to severe disease. The mean PASI score was 18.5 (median 17.0; range: 8.0 - 48.0) and the majority of subjects had a baseline sPGA score of 3 (58.5%; 206/352) or 4 (33.5%; 118/352). The mean affected BSA involvement at baseline was 22.0% (range: 10.0 - 85.0%). The mean NAPSI score at baseline was 4.2. Subjects with scalp PSOR tended to have moderate (44.0%; 155/352) or severe (19.9%; 70/352) involvement at baseline.

The PSOR-related therapies that were used by subjects prior to enrolment were generally well balanced across the 4 treatment groups. Half of all patients (50.0%; 176/352) had previously received systemic treatment for PSOR, and nearly half of those subjects (44.3%; 78/176) had failed 1 or more systemic therapies. Topical dermatological agents had been used by 24.7% (87/352) of patients, while 17.6% (62/352) had been treated previously with MTX and 5.7% (20/352) had prior use of acitretin. In addition, 31.8% (112/352) of subjects had prior exposure to biologics, including 21.6% (102/411) with previous anti-TNF experience and 9.1% (32/352) had a history of ustekinumab use. The incidence of relevant co-morbid conditions was similar in the treatment groups. A past history of hypertension was recorded in 29.0% of all subjects (102/352), 11.6% (41/352) reported hyperlipidaemia and 7.1% (26/352) had type 2 diabetes mellitus. Past history of depression was recorded in 17.3% of patients (61/352).

7.2.1.2.12. Results for the primary efficacy outcome

In Study PSOR-005, the percentage of subjects achieving PASI 75 response at week 16 increased in a dose related manner with APR. A statistically greater proportion of subjects treated with APR 20mg and APR 30mg twice-daily groups achieved a PASI 75 response at week 16 (28.7% [25/87] and 40.9% [36/88], respectively) compared with PBO-treated subjects (5.7%; 5/88). The treatment related difference was 23.1 - 35.2 with 95% CIs supporting the statistically significant observation ($p < 0.0001$ for both pair-wise comparisons). The proportion of subjects reaching PASI 75 response at week 16 was not statistically different in the APR 10mg twice-daily group (11.2%; 10/89) compared to PBO ($p = 0.1846$). The results of the primary analysis were supported by the sensitivity analyses conducted to assess the impact of missing data. Sensitivity analyses included using NRI as alternative method to LOCF for handling missing data, as well as examining the PP population versus ITT.

The beneficial effect of APR 20mg and 30 mg twice daily was consistently seen in all patient subgroups, although there was a trend for a lower PASI 75 response in patients with more severe PSOR at baseline (i.e. PASI score > 20) or in subjects who had failed prior systemic therapies.

7.2.1.2.13. Results for other efficacy outcomes

Similar to the primary efficacy outcome, a statistically greater proportion of subjects treated with APR 20mg twice daily and APR 30mg twice daily compared to PBO achieved a PASI 50 and PASI 90 response at 16 weeks ($p < 0.02$ for all comparisons) (Table 15).

Table 15: Proportion of Subjects Achieving PASI 50 and PASI 90 Response at Week 16 in Study PSOR-005

	Placebo N = 88	APR 10 BID N = 89	APR 20 BID N = 87	APR 30 BID N = 88
Achieved PASI-50 – n(%)	22 (25.0)	34 (38.2)	41 (47.1)	53 (60.2)
Difference in Proportions (95% CI)[a]		13.2 (-0.4, 26.8)	22.1 (8.3, 36.0)	35.2 (21.6, 48.9)
p-value[b]		0.0590	0.0023	< 0.0001
Achieved PASI-90 – n(%)	1 (1.1)	4 (4.5)	8 (9.2)	10 (11.4)
Difference in Proportions (95% CI)		3.4 (-1.5, 8.2)	8.1 (1.6, 14.5)	10.2 (3.2, 17.2)
p-value		0.1776	0.0158	0.0051

APR = apremilast; BID = twice daily; CI = confidence interval; LOCF = last observation carried forward; PASI = psoriasis area 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.

At week 24, PBO subjects who were re-randomised to active treatment with APR (20mg twice-daily or 30mg twice-daily) demonstrated PASI 50 and PASI 75 response rates similar to those for subjects originally randomised to those 2 doses of APR. The rates of PASI 50 response at week 24 (using observed data) were: 33.7% (30/89) in the APR 10mg group, 46.0% (40/87) in the APR 20mg arm, 60.2% (53/88) in the APR 30mg group, 58.8% (20/34) in the PBO→20mg twice-daily group and 66.7% (24/36) in the PBO→30mg twice-daily arm. The rates of PASI 75 response at week 24 (using observed data) were: 15.7% (14/89) in the APR 10mg group, 24.1% (21/87) in the APR 20mg arm, 36.4% (32/88) in the APR 30mg group, 38.2% (13/34) in the PBO→20mg twice-daily group and 41.7% (15/36) in the PBO→30mg twice-daily arm. There was a significant decrease in the number of subjects remaining in the trial from week 24 to 52, which confounds the interpretation of the PASI responses. For example, the rate of PASI 50 response at week 52 was 42.6% (20/47) in the APR 10mg twice daily group, 48.0% (24/50) in the APR 20mg twice daily arm, 72.4% (42/58) in the APR 30mg twice daily group, 55.6% (15/27) in the PBO→20mg twice daily group and 48.1% (13/27) in the PBO→30mg twice daily arm.

Subjects in all APR treatment groups recorded a statistically significant LS mean improvement in PASI score from baseline compared to PBO ($p = 0.0156$ for APR 10mg and $p < 0.0001$ for both APR 20mg and 30mg). At 16 weeks, the mean percentage reduction from baseline in PASI score was -34.0% in the APR 10mg group (baseline mean 18.1), -45.4% in the APR 20mg arm (baseline mean 18.8), -53.2% in the APR 30mg group (baseline mean 19.1) and -20.3% in the PBO group (baseline mean 18.1). For subjects treated with APR, the mean percentage change in PASI continued to decrease (improve) through to week 24 (-43.4% in the 10mg group, -58.4% in the 20mg arm and -66.5% in the 30mg group). PBO subjects re-randomised to APR at week 16 showed rapid improvement by week 24 (-60.9% in the 20mg switch group and -62.9% in the 30mg switch arm). Treatment response was maintained until week 52 for the mean percentage improvement from baseline in the PASI score, for the subset of patients continuing in the extension trial (-57.5% to -67% for the APR 20mg and 30mg treatment groups).

At week 16, a statistically significant greater proportion of subjects treated with APR 20mg twice-daily group (25.0%; 20/80) and APR 30mg twice-daily (33.7%; 28/83) achieved sPGA score of 0 or 1 compared to 12.6% (11/87) in the PBO arm ($p = 0.0402$ and $p = 0.0011$,

respectively). Subjects treated with APR 10mg twice daily did not have a higher rate of sPGA 0 or 1 response at week 16 (10.5%; 9/86) compared with PBO. For patients continuing in the trial, the rate of sPGA response (score of 0 or 1) remained stable at weeks 24 and 52.

Regarding the LS mean percentage change in affected %BSA involvement, all of the APR treatment groups where statistically better versus PBO. At week 16, the LS mean percentage change in affected %BSA was -31.7% in the APR 10mg group ($p = 0.0020$), -49.4% in the APR 20mg arm ($p < 0.0001$) and -56.3% in the APR 30mg group ($p < 0.0001$) versus the PBO arm (-13.2%). Improvements (reduction) in %BSA affected continued past week 16 (-55.3% in the APR 20mg group and -64.3% in the APR 30mg arm at week 24; and -58.3% in the APR 20mg group and -67.3% in the APR 30mg arm at week 52). Once PBO subjects were re-randomised to APR 20mg or 30mg twice daily at week 16, they demonstrated improvements in %BSA affected that matched patients originally randomised to APR (-51.4% in the APR 20mg switch group and -55.2% in the APR 30mg switch arm at week 24). For the treatment switch patients, these improvements appeared to be maintained or improved between weeks 24 and 52 (-67.4% in the APR 20mg switch group and -64.9% in the APR 30mg switch arm at week 52).

The mean DLQI scores at baseline were 10.5, 10.8, 11.6 and 10.4 for subjects randomized to PBO, APR 10mg, APR 20mg and APR 30mg twice daily, respectively. Subjects treated with APR 20mg and 30mg achieved a statistically significant LS mean reduction in the DLQI score at week 16 (-5.9 in the 20mg twice daily dose arm and -4.4 in the 30mg twice daily dose group) compared with PBO (-1.9; $p < 0.0001$ and $p = 0.0047$, respectively). However, patients treated with APR 10mg twice daily did not achieve a statistically better LS mean improvement in the DLQI score at week 16 (-3.2; $p = 0.1322$) compared to PBO. The mean changes from baseline to week 16 in SF-36 scores were statistically different between all dose regimens of APR versus PBO for the MCS score ($p < 0.008$ for all comparisons), but no APR treatment group was statistically better than PBO for the PCS score. The results for health related QOL (DLQI and SF-36 scores) at weeks 24 and 52 showed similar results as observed at week 16.

7.2.2. Other efficacy studies

7.2.2.1. Study PSOR-001

Study PSOR-001 was an open-label, single arm, pilot study, which enrolled 19 subjects with severe plaque PSOR and 17 completed the trial. It was conducted at 3 sites in the USA during 2005. A secondary objective of the study was to evaluate the clinical effects of APR (2 x 10mg tablets taken once daily upon awakening fasted; for 29 days) upon the PASI and sPGA scores, as well as the %BSA affected by PSOR. Three of the 17 evaluable subjects (17.6%) achieved a PASI 50 response at day 29. Nine of 17 patients (52.9%) had at least a 1-point improvement from baseline in their sPGA score at day 29. Ten of the 17 subjects (58.8%) with a PSOR BSA assessment at day 29 showed an improvement from baseline.

7.2.2.2. Study PSOR-003

Study PSOR-003 was a Phase II, randomized, PBO-controlled, double-blind, parallel group trial that enrolled 260 subjects with moderate to severe plaque PSOR (> 6 months immediately prior to enrolment) who were candidates for systemic therapy. The primary objective of the study was to assess the clinical efficacy of 2 doses of APR (20mg once daily and 20mg twice daily) compared with PBO over 12 weeks. The study had 3 phases: a pre-randomisation period of up to 4 weeks, followed by a 12-week treatment period and a 4-week post-treatment observation phase (to monitor for relapse and flare off study medication). At baseline, subjects were required to have PASI score > 10 and BSA involvement > 10%. Study visits were scheduled every 2 weeks during the trial. The study was conducted at 34 sites (28 of which randomised subjects) in Canada, Germany and the Czech Republic between April 2006 and February 2007.

Subjects meeting eligibility criteria were randomized 1:1:1 at baseline via a central system into 1 of 3 treatment groups: APR 20mg twice daily, APR 20mg once daily and PBO. The primary efficacy endpoint of the trial was the proportion of subjects in each group with PASI 75

response at 12 weeks. Based on the available literature, it was estimated that a 25% difference between active (35% response rate) and PBO treatment (10% response rate) might be expected. A 2-group continuity corrected chi-square tests with a 0.025, 2-sided significance level (using the Bonferroni procedure to adjust for the 2 active treatment groups versus PBO to preserve an overall error rate of 0.05, 2-sided) would have 90% power to detect a 25% treatment related difference if the sample size in each group was 68 subjects. However, the study aimed to recruit 85 subjects (255 in total) in each treatment group as the assumed dropout rate was 20%.

A total of 345 subjects were screened for involvement in this study, but 85 subjects were screen failures (32 withdrew consent, 23 did not meet the inclusion criteria, 13 did not meet the exclusion criteria and 17 failed screening for other reasons). A total of 259 subjects (85 in the APR 20mg twice daily group, 87 in the APR 20mg once daily arm and 87 in the PBO group) were randomized and received at least 1 dose of study medication. One subject in the APR 20mg twice daily group was a screen failure but erroneously randomized. This subject did not receive any study medication but was included in the ITT population for efficacy analysis. Overall, 81.9% (212/259) completed the treatment phase: 87.1% (74/86) in the APR 20mg twice daily group, 80.5% (70/87) in the APR 20mg once daily arm and 78.2% (68/87) in the PBO group. The 2 most common reasons for premature discontinuation were AEs (which occurred at a lower incidence in the APR treatment groups [3.5% and 5.7%] versus PBO [8.0%]) and lack of therapeutic effect (which occurred at a lower incidence in the APR 20mg twice daily group [3.5%] versus the 2 other arms [5.7% in both groups]). The majority of randomised subjects entered the follow-up phase (86.5%; 225/260) and most of those subjects completed the follow-up period (82.7%; 215/260). Major protocol deviations that may have impacted upon efficacy assessments were recorded in a lower percentage of subjects in the APR 20mg twice daily group (4.7%; 4/86) compared with the other 2 treatment groups (10.3%; 9/87 in both arms).

The demographic characteristics of subjects at baseline were similar across the 3 treatment groups. In Study PSOR-003, the majority of subjects were Caucasian (96.9%; 251/259) and male (62.9%; 163/259) with a mean age of 46.1 years (range: 19 - 85 years). The mean weight of the enrolled subjects was 86.4 kg (range: 41.0 - 157.0 kg). The treatment groups were also similar with respect to baseline PSOR features. The mean duration of PSOR for all subjects was 19.1 years, and 18.9% (49/259) of patients had concurrent PsA. Baseline PSOR characteristics were consistent with moderate to severe disease. The mean PASI score was 19.5 (range: 10.0 - 49.0) and the majority of subjects had a baseline sPGA score of 3 (59.8%; 155/259). The mean affected BSA involvement at baseline was 29.6% (range: 10.0 - 84.0%). Very few patients had used PSOR-related therapies prior to enrolment (e.g. dermatological agents had only been previously used by 2.3% [6/259) of all patients).

A statistically significant greater proportion of subjects in the APR 20mg twice daily group (24.4%; 21/86) achieved PASI 75 response at week 12 compared with PBO (10.3% [9/87]; p = 0.023). However, the same percentage of subjects in the APR 20mg once daily group achieved PASI 75 at 12 weeks as the PBO group (10.3% [9/87] in both treatment groups). By the end of the observational follow-up phase, the proportion of subjects maintaining PASI 75 response decreased in all treatment groups compared to week 12 (15.1% [13/86] in the APR 20mg twice daily group, 3.4% [3/87] in the APR 20mg once daily arm and 8.0% [7/87] in the PBO group).

Consistent with the primary efficacy endpoint observation, statistically significant improvements were seen with APR 20mg twice daily compared to PBO across the secondary efficacy endpoints including the mean percentage change from baseline to week 12 in PASI score, BSA involvement, sPGA score, rate of PASI 50 and 90 response, as well as DLQI and SF-36 scores, but there was frequently no significant differences between APR 20mg once daily and the PBO group for the various outcomes. At 12 weeks, the mean percentage reduction from baseline in PASI score was -52.1% in the APR 20mg twice daily group, -30.3% in the APR 20mg

once daily arm and -17.4% in the PBO group ($p < 0.001$ and $p = 0.021$, respectively). Regarding the mean percentage change in affected %BSA involvement, the APR 20mg twice daily group was statistically better versus PBO (-30.8% versus -3.2%; $p < 0.001$) but the comparison between APR 20mg once daily (-15.2%) was not statistically superior ($p = 0.104$). The mean reduction from baseline in sPGA score at week 12 for the PBO group was -0.7 points (mean baseline sPGA score 3.2) compared with -1.3 points (mean baseline sPGA score 3.1), which was statistically significant ($p < 0.001$). In the APR 20mg once daily group, the mean decrease in sPGA score was -0.8 from a baseline mean of 3.1, which was not statistically significant ($p = 0.755$). At week 12, a statistically significant greater proportion of subjects treated with APR 20mg twice daily group (57.0%; 48/86) achieved a PASI 50 response compared to 23.0% (20/87) in the PBO arm ($p < 0.001$). Subjects treated with APR 20mg once daily did not have a statistically higher rate of PASI 50 response at week 12 (27.6%; 24/87) compared with PBO ($p = 0.601$). At week 12, 14.0% (12/86) of subjects in the APR 20mg twice daily achieved PASI 90 response versus 5.7% (5/87) in the PBO group and 2.3% (2/87) in the APR 20mg once daily arm. The comparison between APR 20mg twice daily and PBO for the rate of PASI 90 response at 12 weeks was statistically significant ($p = 0.037$). The mean DLQI scores at baseline were 10.6, 11.3 and 11.2 for subjects randomized to PBO, APR 20mg once daily and APR 20mg twice daily, respectively. Subjects treated with APR achieved a statistically significant reduction in the DLQI score at week 12 (-7.0 in the twice daily dose arm and -4.8 in the once daily dose group) compared with PBO (-2.7; $p < 0.001$ and $p = 0.027$, respectively). The mean changes from baseline to week 12 in SF-36 scores (overall, summary scores and each domain) were not statistically different between APR (either dose regimen) and PBO, apart from the MCS and PCS scores for APR 20mg twice daily versus PBO ($p = 0.045$).

7.2.2.3. Study PSOR-004

Study PSOR-004 was a Phase II, open-label trial enrolling 30 subjects with treatment recalcitrant plaque PSOR, which secondarily examined the efficacy of APR. All patients received treatment with APR 20mg twice daily for 84 days (initial 12 week treatment phase), and there was an optional 84-day extension period whereby subjects received either APR 20mg (n = 4) or 30mg twice daily (n = 7). Patients who hadn't achieved PASI 75 response at 12 weeks were dose escalated to APR 30mg twice daily in the 12-week extension period, while responding patients maintained APR 20mg twice daily in the extension phase. The study was conducted at 4 sites in the USA between August 2007 and May 2009. All of the enrolled subjects had prior exposure to systemic treatments for PSOR, and 18 had previous experience with biologic therapies. Many of the subjects had tried multiple prior systemic and/or biologic therapies, meeting the criteria for treatment refractory PSOR at enrolment. The protocol specified main efficacy endpoint was that > 20% of enrolled subjects would achieve at least a 1-point reduction (improvement) from baseline to week 12 their sPGA score. APR met this criterion as 66.7% (20/30) of subjects reached this outcome. During the extension phase, all 4 subjects who received APR 20mg twice daily maintained the 1-point reduction from baseline in their sPGA score, however, 4 of the 7 patients in the APR 30mg twice daily group didn't have sufficient readings to assess maintenance of response. At 12 weeks, 30% (9/30) achieved PASI 75 response and 13.3% (4/30) reached PASI 90 response. All 4 subjects who remained on APR 20mg in the extension phase maintained their PASI 75 response recorded at week 12, until week 24. For the 7 insufficiently responding patients at week 12 who continued into the extension phase on an increased dose of APR (30mg twice daily), 3 had substantial continued improvement (PASI improvement between 50 and 74.4%), 2 had minor improvements (< 5% change from baseline) and 2 showed minor worsening (< 1-point increase in the 72-point PASI score). PASI 75 response was not associated with prior PSOR treatment (number and type of systemic and biologic treatments). Mean and median DLQI scores decreased significantly from baseline to week 12 and 24, but the SF-36 results showed minor worsening with APR treatment over 12 and 24 weeks. Eight of the enrolled subjects had concurrent PsA and 25% (2/8) achieved an

ACR20 response at week 12, and 1 patient continued to maintain that joint response until week 24 (on APR 30mg twice daily).

7.2.3. Analyses performed across trials (pooled analyses and meta-analyses)

The submission contained a comparison and analysis of the results across the 2 pivotal studies in PSOR (Studies PSOR-008 and PSOR-009), but no pooled analysis of the results was provided. The comparison did not reveal any new observations than that demonstrated in the individual trials.

7.2.4. Evaluator's conclusions on clinical efficacy for indication 2: Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

This submission contains 2 pivotal Phase III studies (PSOR-008 and PSOR-009) involving a total of 1275 subjects, and 4 non-pivotal Phase II trials (including a randomized, dose-ranging study PS0R-005) to support the proposed treatment indication of moderate to severe plaque PSOR in adult subjects. The 2 pivotal studies were of similar design and both consisted of a 16-week randomized, double-blind, PBO-controlled phase followed by a 20-week, randomized, double-blind treatment withdrawal period. In this submission, both Phase III PSOR studies submitted a 52-week efficacy report. Both Phase III studies recruited adult patients with moderately to severely active PSOR (well defined and adhered to) of at least 12 months duration prior to screening. Eligible subjects were also required to be candidates for systemic or phototherapy, which is consistent with the requested treatment indication. In both of the Phase III studies, the primary efficacy endpoint was the rate of PASI 75 response assessed at 16 weeks, which is a clinically meaningful outcome. The main supporting Phase II study (PSOR-005) also assessed the primary efficacy outcome of PASI 75 response at 16 weeks but continued collecting data beyond 52 weeks.

This submission is seeking an indication in active PSOR, and in general is consistent with the TGA adopted regulatory guideline pertaining to the requested indication: EU guideline "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriasis" (effective 28 July 2008). In the Phase II and III trials, the choice of clinical and QOL endpoints, as well as the statistical analyses were appropriately performed.

The baseline demographic and disease related characteristics of patients in each of the Phase II and III Studies are similar to those in the anticipated Australian patient cohort, and therefore generalization of these results to the Australian context is expected. However, there are some caveats to the generalizability of the treatment population. For example, all of the trials excluded patients who were at a significant risk of infection, history of major illness including past history of cancer or who had various abnormal laboratory results at baseline (e.g. abnormal haematology or liver function tests, as well as haemoglobin A1c > 9.0%).

The pivotal trials enrolled patients with moderately-severely active PSOR, and demonstrated that APR is an effective treatment in those who are candidates for systemic or phototherapy. The majority of patients (> 90%) had received treatment with at least 1 therapy, of which dermatological agents (> 85%) such as topical CS was the most common. In addition, approximately two-thirds of all patients in the Phase III studies had previously received either systemic therapy (mainly, MTX or CsA) or phototherapy, and about 30% had prior biologic treatment exposure (mainly, anti-TNF drugs). The primary efficacy endpoint of both Phase III studies was the proportion of subjects who achieved a PASI 75 response at 16 weeks, and this was achieved in both trials. In the PSOR-008 Study, more patients treated with APR 30mg twice daily (33.1%; 186/562) achieved this outcome versus 5.3% (15/282) of patients in the PBO group. In the PSOR-009 Study, the PASI 75 response rates showed a similar benefit in favour of APR (28.8% [79/274] with APR 30mg twice daily versus 5.8% [8/137] in the PBO group). The PBO response rates were low in both studies, which is what should be expected in well-conducted PSOR studies using PASI 75 response rate as the primary efficacy outcome. Many

secondary efficacy measures examining other clinical outcomes (such as significant improvements in sPGA scores, PSOR affected %BSA and mean change from baseline in PASI score) as well as QOL endpoints (such as the mean changes from baseline in DLQI and SF-36 MCS scores) also demonstrated clinically significant changes with APR. Additionally, improvements in measures of disease activity affecting the nails and scalp (NAPSI scores and scPGA change) were also attained with APR therapy. In both Phase III PSOR studies, an important secondary endpoint was the rate and time to loss of treatment effect upon APR withdrawal. Both trials showed that continuation of APR was superior to treatment withdrawal in maintaining clinically significant improvements beyond an initial treatment course. Similarly, the time to loss of treatment effect was much shorter in patients who were withdrawn from APR versus continued therapy. In Study PSOR-008, the median time to first loss of PASI 75 response was 5.1 weeks for PBO (n = 64 of 77) and 17.7 weeks for APR 30mg twice daily (n = 40 of 77; $p < 0.0001$). In Study PSOR-009, the PASI 50 responders who were re-randomized to PBO at week 32 lost 50% of their improvement at a median time of 12.4 weeks for PBO (n = 35 of 62) compared with 21.9 weeks for continued APR 30mg twice daily (n = 7 of 61; $p < 0.0001$).

In the dose-ranging Phase II Study PSOR-005, there was a clear dose response relationship for APR over the studied dose range of 10mg twice daily, 20mg twice daily and 30mg twice daily. A statistically greater proportion of subjects treated with APR 20mg and APR 30mg twice daily in Study PSOR-005 achieved a PASI 75 response at week 16 (28.7% [25/87] and 40.9% [36/88], respectively) compared with PBO-treated subjects (5.7%; 5/88). However, the proportion of subjects reaching PASI 75 response at week 16 was not statistically different in the APR 10mg twice daily group (11.2%; 10/89) compared to PBO ($p = 0.1846$). The majority of secondary efficacy endpoints supported the observation that APR 10mg twice daily was of no significant benefit compared with PBO, but APR doses of 20mg and 30mg twice daily demonstrated a consistent dose-response relationship. In addition, for subjects who continued in that trial, clinical response was maintained for up to 52 weeks of treatment. The 3 other Phase II studies (2 of which were open-label, and 1 randomized) supported the observation that APR therapy results in clinically meaningful improvements in PSOR disease activity. Clinical response to APR appears to onset after 4 weeks of therapy, and peaks 16 weeks after treatment initiation.

Overall, the data in this submission supports the efficacy of APR in the treatment of active PSOR from a clinical perspective (i.e. in beneficially treating the symptoms [pruritus] and signs of PSOR [PASI scores and %BSA affected]) in those with moderate and severely active disease at baseline, who are candidates for systemic or phototherapy. Subgroup analyses across multiple demographic and disease characteristics were performed and there was no clear association between PSOR severity, prior systemic treatment and subject BMI at baseline in predicting response to APR but this may require a larger number of subjects in each subgroup to be elucidated.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by completion of the AE Case Report Form (CRF) and physical examination at baseline; weeks 4, 16, 24 and 28 weeks; and every 12 weeks thereafter.

- AEs of particular interest, including hypersensitivity, infections (serious and opportunistic), major adverse cardiovascular events, psychiatric disorders and malignancies were assessed by CRF and physical examination as per the schedule for general AE evaluation.
- Laboratory tests, including haematology, biochemistry and urinalysis were performed at baseline and every 4 weeks until week 28, and then every 12 weeks thereafter.
- Vital signs such as blood pressure, heart rate, weight and temperature were performed at each scheduled study visit.

For the Phase III PsA dataset (Studies PSA-002, -003, -004 and -005), safety analyses were provided for 4 analysis periods: weeks 0 - 16, weeks 0 - 24, weeks 0 - 52 and the total APR exposure period. For the Phase III PSOR dataset (PSOR-008 and PSOR-009), safety analyses were provided for 3 analysis periods: weeks 0 - 16, weeks 0 to 52 and the total APR exposure period. The APR exposure period encompassed all safety data from the first dose of APR up to week 52 (i.e., data from weeks 0 to 52 for all subjects initially randomized to APR, data from weeks 16 to 52 [up to 36 weeks exposure] for PBO-treated subjects who entered EE at week 16, and data from weeks 24 to 52 [up to 28 weeks exposure] for PBO treated subjects who were re-randomized to APR at week 24). The analyses of AEs and markedly abnormal clinical laboratory values were conducted using subject incidence, as well as using the Exposure-Adjusted Incidence Rate (EAIR) expressed as the number of events occurring per 100 patient-years (PY).

Blinded independent adjudication of treatment emergent AEs of Major Adverse Cardiac Events (MACE), malignancies and serious infections (including opportunistic infection) recorded in any subject enrolled in any of the Phase II or III studies was also performed. These results will be discussed in the serious adverse event section of this report (section 8.4.3).

8.1.2. Pivotal studies that assessed safety as a primary outcome

No studies in either the PsA or PSOR program were pivotal studies that assessed safety as a primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies that provided safety data are as follows:

- For the treatment indication of PSOR there were 2 open-label Phase II trials (Studies PSOR-001 and PSOR-004) and 2 randomized Phase II trials (Studies PSOR-003 and PSOR-005).
- For the treatment indication of PsA, Study PSA-001 which was Phase II dose-ranging trial provided safety data on APR, as per the same assessments as the Phase III PsA program.

8.1.4. Other studies evaluable for safety only

In all of the other treatment indication studies (BCT-001, ASTH-001 and RA-002), APR was well tolerated in general with gastrointestinal AEs (such as nausea, diarrhoea and vomiting) occurring more frequently in subjects receiving APR than those taking PBO. Most of the AEs were mild-to-moderate in severity. Few subjects discontinued APR to AEs, and most discontinuations were due to disease flare or insufficient efficacy. The types of AEs observed in these 3 studies were consistent with the safety profile of APR. Furthermore, the frequency of AEs reported between PBO and APR treated subjects had a similar fold increase to that observed in the PsA and PSOR trials. There were no unusual or unexpected safety findings in these 3 studies.

8.1.4.1. Study BCT-001

This was a Phase II, multicentre, randomized, PBO-controlled, double-blind, parallel-group study of APR in the treatment of Behçet's disease. The study included a 12-week PBO-controlled treatment phase and a 12-week blinded extension period. A total of 56 subjects were randomized to PBO and 55 subjects were randomized to APR 30mg twice daily. The mean

duration of follow-up in the treatment phase was 10.65 weeks in the PBO group and 11.43 weeks in the APR arm. In the 12-week extension phase, subjects who had received PBO during the initial treatment phase were switched to APR 30mg twice daily. Subjects who were randomized to APR continued to receive the same dose of APR. Mean exposure to APR in the extension phase was 12.1 weeks in the PBO to APR switch group and 22.0 weeks in the continued APR treatment group.

8.1.4.2. Study ASTH-001

Study ASTH-001 was a Phase II, multicentre, randomized, PBO-controlled, parallel-group, exercise-challenge study comparing 2 oral doses of APR with PBO administered for 29 days in subjects with mild asthma. A total of 73 subjects were enrolled and randomized to treatment: 26 subjects received APR 20mg once daily, 23 subjects received APR 20mg twice daily and 24 subjects received PBO. The mean duration of treatment was 28.2 days, 27.7 days, and 28.5 days for the APR 20mg once daily, APR 20mg twice daily and PBO groups, respectively.

8.1.4.3. Study RA-002

Study RA-002 was a Phase II, multicentre (43 sites in 3 countries), randomized, PBO-controlled, double-blind, parallel-group study designed to assess the efficacy and safety of 2 doses of APR compared to PBO in the treatment of active RA receiving concomitant stable doses of MTX. The study included a 24-week PBO-controlled treatment phase (with provision for early escape at week 16 in non-responding subjects) followed by another 24-week, double-blind active treatment phase. A total of 79 subjects were randomized to PBO, 82 subjects were randomized to APR 20mg twice daily and 76 subjects were randomized to APR 30mg twice daily. The trial failed to demonstrate that APR (either dose) versus PBO could produce a statistically significant reduction in the signs and symptoms of RA (using ACR response criteria) and functional improvement (using HAQ-DI score changes) at 16 - 24 weeks of treatment follow-up. The study was halted at week 24 due to the lack of treatment efficacy. Of the 237 subjects randomised at baseline, 198 (83.5%) completed the PBO controlled phase (week 24 visit), including 88.6% of patients in the PBO group, 81.7% of subjects in the APR 20mg arm and 80.3% of patients in the APR 30mg group.

8.1.4.4. Clinical pharmacology studies

The clinical pharmacology program consisted of 16 studies that enrolled 422 healthy subjects, 15 patients with either PsA or RA, 8 subjects with severe renal impairment and 16 subjects with hepatic impairment. In the clinical pharmacology studies, 251 subjects received either a single dose or single doses of APR separated by a washout period, and 104 subjects received between 2 - 7 days of APR dosing, 35 subjects took APR for 8 - 13 days and 44 subjects received > 14 days of therapy. The clinical pharmacology studies will be presented as a dataset in this report.

8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.3. Patient exposure

This submission contained a total of 14 Phase II or III studies (5 in PsA, 6 in PSOR, 1 in RA, 1 in Behçet's disease and 1 in asthma) as the primary supporting database for clinical safety. In these trials, the following APR dosage regimens were evaluated: 10mg twice daily, 20mg once daily, 20mg twice daily, 40mg once daily and 30mg twice daily. The safety cut-off dates for inclusion of safety information are March 1, 2013 for the PsA dataset and January 11, 2013 for the PSOR dataset.

A summary of the total exposure to APR, which includes subjects initially randomized to APR in all studies as well as PBO-treated subjects who switched to APR is presented in Table 16. A total

of 4089 subjects have received at least 1 dose of APR. A total of 3049 (74.6%) subjects have received APR for at least 24 weeks, including 1024 (70.6%) subjects who received APR 20mg twice daily and 1930 (81.9%) subjects who received APR 30mg twice daily. A total of 1631 (39.9%) subjects have been exposed to APR for at least 52 weeks in completed and ongoing studies, including 510 (35.2%) subjects treated with APR 20mg twice daily and 1107 (47.0%) subjects treated with APR 30mg twice daily (as of the cut-off dates for this submission).

Table 16: Summary of Total Patient Exposure to Apremilast

	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.

8.3.1. PsA phase III data pool

A total of 1945 subjects are included in the treated Phase III PsA dataset, including 972 subjects who have received APR 20mg twice daily and 973 subjects who have received APR 30mg twice daily. Overall, 1607 (82.6%) subjects have received APR for at least 24 weeks, including 790 (81.3%) subjects who have received APR 20mg twice daily and 817 (84.0%) subjects who have received APR 30mg twice daily. A total of 962 (49.5%) subjects had been exposed to APR for at least 52 weeks, including 467 (48.0%) subjects in the APR 20mg twice daily group and 495 (50.9%) subjects in the APR 30mg twice daily cohort. A summary of the total exposure to APR in the Phase 3 PsA dataset, which includes subjects initially randomized to APR, as well as PBO patients who switched to APR, is presented in Table 17. In the Phase III PsA dataset, a total of 648 subjects received APR with concomitant DMARD therapy (including 329 subjects treated with APR 20mg twice daily and 319 subjects treated with APR 30mg twice daily). A total of 700 subjects received APR without concomitant DMARD treatment.

Table 17: Summary of Total Patient Exposure to Apremilast in Phase 3 Psoriatic Arthritis Dataset

Exposure Category [a]	20 mg BID (N=972) n (%)	30 mg BID (N=973) n (%)	Apremilast Total (N=1945) n (%)
>= 1 day	972 (100.0)	973 (100.0)	1945 (100.0)
>= 4 Weeks	946 (97.3)	933 (95.9)	1879 (96.6)
>= 8 Weeks	910 (93.6)	901 (92.6)	1811 (93.1)
>= 12 Weeks	884 (90.9)	884 (90.9)	1768 (90.9)
>= 24 Weeks	790 (81.3)	817 (84.0)	1607 (82.6)
>= 32 Weeks	673 (69.2)	696 (71.5)	1369 (70.4)
>= 52 Weeks	467 (48.0)	495 (50.9)	962 (49.5)
>= 78 Weeks	168 (17.3)	178 (18.3)	346 (17.8)
>= 91 Weeks	79 (8.1)	85 (8.7)	164 (8.4)
>= 104 Weeks	30 (3.1)	32 (3.3)	62 (3.2)
Subject Years			
n	972	973	1945
Mean	0.96	0.97	0.97
Std	0.526	0.524	0.525
25% Percentile	0.54	0.54	0.54
Median	0.98	1.00	0.99
75% Percentile	1.27	1.28	1.27
Min	<= .01	<= .01	<= .01
Max	2.49	2.50	2.50

8.3.2. PSOR phase III data pool

A total of 1184 subjects in the Phase III PSOR dataset received APR 30mg twice daily, which includes subjects initially randomized to APR, as well as PBO subjects who were switched to receive APR. Overall, 968 (81.8%) subjects with PSOR have received APR 30mg twice daily for at least 24 weeks, and a total of 564 (47.6%) subjects had been exposed to the same dose of APR for at least 52 weeks. A summary of exposure to APR in the Phase III PSOR dataset is provided in Table 18.

Table 18: Summary of Total Patient Exposure to Apremilast in Phase III Psoriasis Dataset

	Subjects as Initially Treated at Week 0		Apremilast Subjects as Treated
Exposure Category [a]	Placebo (N=418) n (%)	30 mg BID (N=832) n (%)	30 mg BID (N=1184) n (%)
>= 1 day	418 (100.0)	832 (100.0)	1184 (100.0)
>= 4 Weeks	397 (95.0)	792 (95.2)	1137 (96.0)
>= 8 Weeks	377 (90.2)	766 (92.1)	1101 (93.0)
>= 12 Weeks	363 (86.8)	752 (90.4)	1072 (90.5)
>= 24 Weeks	0 (0.0)	687 (82.6)	968 (81.8)
>= 32 Weeks	0 (0.0)	598 (71.9)	854 (72.1)
>= 52 Weeks	0 (0.0)	431 (51.8)	564 (47.6)
>= 78 Weeks	0 (0.0)	165 (19.8)	197 (16.6)
>= 91 Weeks	0 (0.0)	66 (7.9)	72 (6.1)
>= 104 Weeks	0 (0.0)	24 (2.9)	24 (2.0)
Subject Years			
n	418	832	1184
Mean	0.28	0.98	0.95
Std	0.075	0.531	0.511
25% Percentile	0.30	0.54	0.54
Median	0.31	1.00	0.96
75% Percentile	0.31	1.40	1.33
Min	<= .01	<= .01	<= .01
Max	0.34	2.17	2.17

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

8.4.1.1.1. Phase 3 PsA studies

Because incidence rates for common AEs are best estimated using PBO-controlled studies, an emphasis on the data for subjects-as-treated during weeks 0 - 16 of the PBO-controlled period of the Phase III PsA dataset will be outlined. A higher proportion of subjects treated with APR (51.9% [351/676] in the 20mg twice daily group and 54.3% [365/672] in the APR 30mg twice daily arm) reported at least 1 AE during the first 16 weeks of follow-up than those who received PBO (42.9%; 288/671). Table 19 shows the most frequently recorded AEs for weeks 0 - 16 of the Phase III PsA dataset. Diarrhoea, nausea and headache were the most frequently reported AEs and these occurred at a higher incidence in the APR treatment groups and appeared to be

dose-dependent. Upper Respiratory Tract Infections (URTI), vomiting and dyspepsia were also more frequently reported in the APR treatment arms compared to PBO-treated subjects. Nasopharyngitis was reported in a higher percentage of APR 20mg twice daily treated subjects compared to PBO-treated subjects; however, incidence rates were similar between the APR 30mg and PBO treatment arms.

Table 19: Most Frequent AEs (> 2% incidence in any treatment group) between Weeks 0 and 16 in Phase III PsA Dataset

	Subjects as Initially Treated at Week 0							
	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	
Preferred Term[3]	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
Diarrhoea	17 (2.5)	8.9	66 (9.8)	36.4	103 (15.3)	60.6	169 (12.5)	48.1
Nausea	26 (3.9)	13.7	64 (9.5)	35.3	101 (15.0)	59.4	165 (12.2)	46.9
Headache	24 (3.6)	12.7	44 (6.5)	23.6	66 (9.8)	36.8	110 (8.2)	30.1
Upper respiratory tract infection	16 (2.4)	8.4	31 (4.6)	16.2	27 (4.0)	14.4	58 (4.3)	15.3
Vomiting	5 (0.7)	2.6	16 (2.4)	8.3	21 (3.1)	11.1	37 (2.7)	9.7
Nasopharyngitis	12 (1.8)	6.2	17 (2.5)	8.8	15 (2.2)	7.9	32 (2.4)	8.3
Hypertension	15 (2.2)	7.8	11 (1.6)	5.6	13 (1.9)	6.8	24 (1.8)	6.2
Dyspepsia	8 (1.2)	4.2	19 (2.8)	9.9	11 (1.6)	5.8	30 (2.2)	7.8
Abdominal pain upper	1 (0.1)	0.5	14 (2.1)	7.2	18 (2.7)	9.5	32 (2.4)	8.4
Abdominal pain	8 (1.2)	4.1	9 (1.3)	4.6	15 (2.2)	7.9	24 (1.8)	6.2

The majority of AEs (particularly, gastrointestinal AEs and headache) in the APR treated subjects had an onset within 4 weeks of starting treatment, were of mild or moderate severity and resolved within 15 days. The safety profile of APR was comparable in subjects with or without concomitant DMARD. Between weeks 0 - 24 and 0 - 52, the incidence of AEs increased but a slower rate than that observed during the first 16 weeks of therapy. During the APR-exposure period for the PsA Phase III dataset, the overall incidence of AEs was 68.2% (663/972; EAIR of 158.6 per 100 patient years [PY]) in the APR 20mg group and 70.3% (684/973; EAIR of 174.0 per 100 PY) in the APR 30mg arm. However, the increased frequency of AEs is not unexpected given the greater duration of exposure to APR and the increased number of subjects receiving APR as a result of PBO-treated subjects switching to APR treatment arm after week 24. The types of AEs reported in the APR-exposure period were similar to those reported during the PBO-controlled phase – diarrhoea (11.4% in the APR 20mg group and 15.0% in the APR 30mg arm), nausea (9.3% in the APR 20mg group and 14.6% in the APR 30mg arm), URTI (9.5% in the APR 20mg group and 8.7% in the APR 30mg arm), headache (7.5% in the APR 20mg group and 10.4% in the APR 30mg arm) and nasopharyngitis (6.7% in the APR 20mg group and 5.9% in the APR 30mg arm).

8.4.1.1.2. Phase III PSOR studies

A higher percentage of subjects treated with APR 30mg twice daily (68.9%; 573/832) reported at least 1 AE during the first 16 weeks of follow-up in the Phase III PSOR studies than those who received PBO (57.2%; 239/418). Table 20 shows the most frequently recorded AEs for weeks 0 - 16 of the Phase III PSOR dataset. Diarrhoea, nausea, URTI and headache were among the most

frequently reported AEs and these occurred at a higher incidence in the APR treated subjects. Nasopharyngitis was also common but reported at a similar incidence in the APR and PBO treatment groups. The majority of common AEs had an onset within 4 weeks of starting study treatment, were of mild or moderate severity and resolved within 15 days.

Table 20: Most Frequent AEs (> 2% incidence in any treatment group) between Weeks 0 and 16 in Phase III PSOR Dataset

	Subjects as Initially Treated at Week 0							
	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	
Preferred Term[3]	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
Diarrhoea	17 (2.5)	8.9	66 (9.8)	36.4	103 (15.3)	60.6	169 (12.5)	48.1
Nausea	26 (3.9)	13.7	64 (9.5)	35.3	101 (15.0)	59.4	165 (12.2)	46.9
Headache	24 (3.6)	12.7	44 (6.5)	23.6	66 (9.8)	36.8	110 (8.2)	30.1
Upper respiratory tract infection	16 (2.4)	8.4	31 (4.6)	16.2	27 (4.0)	14.4	58 (4.3)	15.3
Vomiting	5 (0.7)	2.6	16 (2.4)	8.3	21 (3.1)	11.1	37 (2.7)	9.7
Nasopharyngitis	12 (1.8)	6.2	17 (2.5)	8.8	15 (2.2)	7.9	32 (2.4)	8.3
Hypertension	15 (2.2)	7.8	11 (1.6)	5.6	13 (1.9)	6.8	24 (1.8)	6.2
Dyspepsia	8 (1.2)	4.2	19 (2.8)	9.9	11 (1.6)	5.8	30 (2.2)	7.8
Abdominal pain upper	1 (0.1)	0.5	14 (2.1)	7.2	18 (2.7)	9.5	32 (2.4)	8.4
Abdominal pain	8 (1.2)	4.1	9 (1.3)	4.6	15 (2.2)	7.9	24 (1.8)	6.2

Between baseline and week 52, the proportion of subjects experiencing at least 1 AE increased but a slower rate than that observed during the first 16 weeks of therapy. During the APR-exposure period for the PSOR Phase III dataset, the overall incidence of AEs was 80.5% (953/1184) in the APR 30mg twice daily treated subjects at an EAIR of 287.4 per 100 PY. The types of AEs reported in the APR-exposure period were similar to those reported during the PBO-controlled phase – diarrhoea (17.6% - EAIR of 22.1 per 100 PY), URTI (16.9% - EAIR of 20.7 per 100 PY), nausea (15.9% - EAIR of 19.6 per 100 PY), nasopharyngitis (15.0% - EAIR of 17.8 per 100 PY) and headache (14.6% - EAIR of 16.7 per 100 PY).

8.4.1.2. Other studies

In the clinical pharmacology studies (pooled dataset), 60.6% of all subjects (264/436) reported at least 1 AE. A treatment and dose-dependent trend was observed in the incidence of AEs. The incidence of AEs was 27.8% (30/108) in the PBO treated subjects, 42.0% (47/112) in the APR < 20 mg/day cohort, 31.1% (42/135) in the APR 30mg/day group, 50.7% (34/67) in the APR 40mg/day patients, 88.9% (8/9) in the titrated APR 40mg/day subjects, 78.1% (89/114) in the APR 60mg/day group and 89.7% (78/87) in the APR 80mg/day treated subjects. The most frequently reported AEs were headache, nausea, diarrhoea, vomiting and dizziness, which correspond with the data in the Phase III trials. The Phase II studies in PsA and PSOR showed a similar finding of treatment and dose-related AEs. In Study BCT-001, 89.1% of subjects in the APR treatment groups recorded at least 1 AE – most commonly, headache, nausea and diarrhoea. In Study ASTH-001, 71.2% (52/73) of subjects reported at least 1 AE – most commonly, headache, nasopharyngitis and diarrhoea. A similar incidence and type of AEs was observed in the RA trial as well.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

8.4.2.1.1. Phase III PsA studies

In the Phase III PsA trial dataset, treatment related AEs (i.e. reasonably related according to site investigator) were summarised over the 4 analysis periods. A higher proportion of subjects in the APR treatment groups (25.3% [171/676] of patients in the APR 20mg twice daily group and 33.9% [228/672] of subjects in the APR 30mg twice daily arm) experienced at least 1 treatment related AE up until week 16 compared with 16.1% (108/671) of subjects in the PBO group. The most frequent type of treatment related AEs was gastrointestinal disorders which affected 27.1% (182/672) of patients in the APR 30mg twice daily group, 16.7% (113/676) of subjects in the APR 20mg twice daily arm and 6.9% (46/671) of subjects in the PBO group. The most commonly reported type of gastrointestinal disorder was diarrhoea followed by nausea. Through to week 16, the proportion of subjects experiencing at least 1 infection was comparable across the treatment groups affecting 3.6% (24/671) of subjects in the PBO group, 3.0% (20/676) of patients in the APR 20mg arm and 3.1% (21/672) of subjects in the APR 30mg group.

Consistent with week 16 results, the proportion of subjects in the APR groups reporting 1 or more treatment related AE through to week 24 was higher compared with PBO. Through to week 52, 31.3% (304/972) of the subjects in the APR 20mg group and 37.7% (367/973) of the subjects in the APR 30mg arm experienced at least 1 treatment related AE. The types of AEs observed through to week 24 and 52 were similar to those seen up to week 16.

8.4.2.1.2. Phase III PSOR studies

In the Phase III PSOR study dataset, a higher proportion of subjects in the APR 30mg twice daily treatment group (39.7%; 330/832) experienced at least 1 treatment related AE up until week 16 compared with 20.8% (87/418) of subjects in the PBO group. The most frequent type of treatment related AEs was gastrointestinal disorders which affected 30.8% (256/832) of patients in the APR group and 11.2% (47/418) of subjects in the PBO group. The most commonly reported type of gastrointestinal disorder was diarrhoea followed by nausea. Through to week 16, the proportion of subjects experiencing at least 1 infection was slightly higher in the APR treatment group (6.0%; 50/832) compared to the PBO group (4.1%; 17/418).

At week 52, 45.7% (380/832) of subjects treated with APR 30mg twice daily experienced at least 1 treatment related AE. The types of AEs observed through to week 52 were similar to those seen up to week 16.

8.4.2.2. Other studies

In the clinical pharmacology studies (pooled dataset), 46.1% of all subjects (201/436) recorded at least 1 drug related AE. A treatment and dose-dependent trend was observed in the incidence of drug related AEs. In general, the incidence of drug related AEs was 6.5% (7/108) in the PBO treated subjects, 29.5% (33/112) in the APR < 20 mg/day cohort, 13.3% (18/135) in the APR 30mg/day group, 38.8% (26/67) in the APR 40mg/day patients, 66.7% (6/9) in the titrated APR 40mg/day subjects, 63.2% (72/114) in the APR 60mg/day group and 79.3% (69/87) in the APR 80mg/day treated subjects. The most frequently reported AEs were headache, nausea, diarrhoea, vomiting and dizziness, which correspond with the data in the Phase III trials. The Phase II studies in PsA and PSOR showed a similar finding of treatment and dose-related drug related AEs. In Study BCT-001, > 50% of subjects in the APR treatment groups recorded at least 1 drug related AE – most commonly, nausea and headache. In Study ASTH-001, 50.6% (37/73) of subjects reported at least 1 drug related AE – most commonly, headache, nasopharyngitis and diarrhoea. A similar incidence and type of drug related AEs was observed in the RA trial as well.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

8.4.3.1.1. Phase III PsA studies

One death was recorded in the Phase III PsA trials. This involved a [information redacted] subject randomized to APR 20mg twice daily in Study PSA-002 who died of multi-organ failure on study day 73. The subject was diagnosed with vitamin B12 deficiency anaemia prior to receiving her first dose of APR. The investigator reported the cause of death as vitamin B12 deficiency attributable to the MTX induced folic acid deficiency. The causality relationship between this death and APR (as well as other therapy) remains unclear.

Between weeks 0 and 16, the proportion of subjects who recorded SAEs in the Phase III PsA dataset was low and similar in each treatment arm: 3.3% (22/671) in the PBO group, 2.4% (23/972) in the APR 20mg twice daily cohort and 2.2% (21/973) in the APR 30mg twice daily group. Most types of SAEs were single case events. The only SAEs reported in > 2 subjects were PsA (3 subjects in the PBO group, and 1 subject in each APR arm), acute myocardial infarction or ischaemia (4 subjects in the APR 20mg group and 1 PBO patient) and hypertensive crisis (2 subjects in the PBO group and 1 APR 30mg twice daily patient). There were also 2 cases each of acute pancreatitis (both in the PBO group), atrial fibrillation (both in the APR 30mg group) and deep vein thrombosis (both in the APR 30mg arm).

For weeks 0 - 24 and weeks 0 - 52, the number of subjects experiencing SAEs was similar between the APR 20mg and APR 30mg treatment arms (approximately 4 - 5% incidence). During the APR-exposure period for the PsA Phase III dataset, a slightly higher frequency of SAEs (6.2% [60/972] in the APR 20mg group and 5.9% [57/973] in the 30mg arm) was reported. However, the small increased frequency of SAEs is not unexpected given the greater duration of exposure to APR and the increased number of subjects receiving APR as a result of PBO-treated subjects switching to APR treatment arm after week 24. Overall, SAEs were infrequent in both the APR 20mg and APR 30mg treatment arms with an EAIR of 7.2 events per 100-subject years and 7.5 events per 100-subject years, respectively. No single SAE occurred with an EAIR greater than 0.5 events to 100-subject years. The types of SAEs reported in the APR-exposure period were similar to those reported during the PBO-controlled phase and included PsA, atrial fibrillation, cholelithiasis, depression, acute myocardial infarction/ischemia, breast cancer, suicide attempt, hypertension, and osteoarthritis.

8.4.3.1.2. Phase III PSOR studies

A total of 3 deaths have been reported in the Phase III PSOR studies (2 in PSOR-008 and 1 in PSOR-009). One of the subjects [information redacted]was found dead at home on study day 111, 7 days after taking their last dose of APR 30 mg. Autopsy revealed diffuse lung congestion and bilateral pulmonary oedema presumed secondary to acute cardiac failure in association with sleep apnoea and morbid obesity (BMI 41 kg/m^2). Another subject [information redacted] who was randomised to PBO committed suicide via [information redacted] on study day 55. The subject had a past history of bipolar disorder, previous suicide attempts, alcohol abuse and an unstable family situation.[4] In Study PSOR-009, a [information redacted] subject died of intracranial haemorrhage on study day 354 (severe headache and unresponsive in study day 352). The patient took APR for 225 days followed by PBO for 112 days. Considering the temporal relationship between the onset of intracranial haemorrhage and the last dose of APR, the death is unlikely to be related to APR.

Between weeks 0 and 16, the proportion of subjects who recorded SAEs in the Phase III PSOR dataset was low and similar in each treatment arm: 2.6% (11/418) in the PBO group and 1.9%

[4] One subject completed suicide, while a second subject was considered as a completed suicide by the FDA. Both subjects were on placebo.

(22/1184) in the APR 30mg twice daily group. Nearly all of the SAEs were single case events. There were 2 cases each of syncope (both occurred in the PBO group) and abdominal pain (both occurred in the APR group). Between weeks 0 and 52, SAEs were recorded by approximately 5% of patients treated with APR, and the type of SAEs was not significantly different from that observed in the first 16 weeks of treatment. During the APR-exposure period for the PSOR Phase III dataset, SAEs affected 5.7% (68/1184) of subjects treated with APR 30mg twice daily, at an EAIR of 6.2 per 100-subject years. The types of SAEs reported in the APR-exposure period were similar to those reported during the PBO-controlled phase and included PSOR, PsA, cholelithiasis, nephrolithiasis, acute myocardial infarction/ischemia, coronary artery disease, hypertension and osteoarthritis.

8.4.3.1.3. Serious adverse events of special interest (Adjudicated analysis)

8.4.3.1.3.1. Serious Infections including Tuberculosis and Opportunistic Infections

A total of 18 subjects recorded a serious infection in the overall APR exposure dataset: 2 PBO-treated subjects, 6 given APR 20mg twice daily and 10 who received APR 30mg twice daily. No serious infections were reported for subjects enrolled in the APR 10mg twice daily, APR 20mg once daily or APR 40mg once daily treatment arms.

There were 3 cases of systemic opportunistic infections which included single cases of Rothia species-related tenosynovitis following a puncture wound, Herpes Zoster with associated viral meningitis, and MRSA-related naso-facial cellulitis/abscess. There were also 3 cases of non-systemic (localised) opportunistic infections which consisted of 2 cases of bacterial pneumonia and a single case of Clostridium difficile infection. The 12 cases of non-opportunistic, serious infections included 3 cases each of appendicitis and pneumonia, 2 cases of cellulitis and single cases of an abdominal abscess, gastroenteritis, anal abscess and empyema.

Ten of the 18 cases of serious infections reported in the overall APR exposure dataset occurred during the PsA Phase III Studies. Serious infections were reported in 2 PBO-treated subjects, 2 subjects from the APR 20mg twice daily treatment arm, and 6 subjects in the APR 30mg twice daily treatment group.

Cases of TB were analysed separately from serious infections and were not independently adjudicated. Screening for latent TB was not required for the Phase III studies and was left to the investigator's judgement; however, all enrolled subjects received a chest X-ray and were questioned to exclude active TB. Also, subjects with active TB, or a history of incompletely treated TB, were excluded from the studies.

A total of 20 subjects with a medical history significant for TB were included in the Phase III PsA dataset (7 PBO-treated subjects, 5 in the APR 20mg group and 8 in the APR 30mg arm). In addition, 12 subjects had a medical history of a positive PPD. No cases of TB or TB reactivation were reported in either the PBO-controlled period or during the APR-exposure period for the Phase III PsA dataset. Similarly, no cases of TB or TB reactivation was reported in the overall APR exposure cohort, despite the enrolment of 23 subjects with a reported medical history of TB and 14 subjects with a medical history of positive PPD.

Overall, the results from both data pools, including EAIRs, suggest no appreciative differences between PBO and APR adjudicated events of serious infections (opportunistic and non-opportunistic), including cases of TB or TB reactivation. Additionally, the overall number of serious infections was relatively small in light of the underlying diseases, concomitant medications, and potential immunosuppressive effects of APR. These data do not demonstrate an increased risk of serious infections with APR therapy.

8.4.3.1.3.2. Major Adverse Cardiac Events (MACE)

AEs related to MACE included sudden un-witnessed death, cardiovascular death (i.e. sudden cardiac death, death due to MI, death due to heart failure, death due to stroke, death due to other cardiovascular causes), MI, and non-fatal stroke. Potential MACE was defined as unstable

angina requiring hospitalization, coronary re-vascularisation procedures, transient ischemic attack (TIA), re-hospitalization for recurrent ischemia, embolic events, and deep vein thrombosis.

Using the overall APR dataset, a total of 66 subjects reported events that were identified for adjudication as MACE or potential MACE: 8 subjects (0.6% of 1411) in the PBO group, 26 patients (1.8% of 1450) in the APR 20mg twice daily arm and 32 subjects (1.4% of 2357) in the APR 30mg twice daily treatment arm. Cases of MACE for adjudication were slightly more common in the PSOR studies (35 subjects in total versus 31 patients in the PsA dataset). In total, 13 of the 66 reported cases were subsequently adjudicated to be MACE (i.e. relatively small numbers overall) and all were attributed to cases of MI. The calculated EAIRs for adjudicated MACE were similar across the PBO (1/1411; 0.1%), APR 20mg (5/1450; 0.3%) and APR 30mg (7/2357; 0.3%) treatment arms at 0.2, 0.4, and 0.3 events per 100 PY, respectively. Events adjudicated as potential MACE were 22 in total: 0.1% of subjects (2/1400; 0.5 per 100 PY) in the PBO group, 0.5% of patients (7/1450; 0.6 per 100 PY) in the APR 20mg twice daily arm and 0.6% (13/2357; 0.6 per 100 PY) in the APR 30mg twice daily group. Four of the adjudicated cases of potential MACE in APR treated individuals were attributed to single cases of unstable angina requiring a revascularization procedure, TIA, DVT, and an embolic event. For 9 of the 66 subjects (2 in the PBO group, 3 in the APR 20mg arm and 4 in the APR 30mg group) there was insufficient information to evaluate for MACE.

8.4.3.1.3.3. Malignancies

Using the overall APR dataset, a total of 52 subjects recorded events that were identified for adjudication as malignancies: 7 subjects (0.5% of 1411) in the PBO group, 16 patients (1.1% of 1450) in the APR 20mg twice daily arm and 29 subjects (1.2% of 2357) in the APR 30mg twice daily treatment arm. Three subjects (all treated with APR) had AEs that were not evaluable as either a tissue biopsy was not taken or the clinical presentation could not be confirmed in the source notes. A total of 46 cases were adjudicated as malignancy events for the overall APR exposure cohort. Malignancy events were reported in the PBO (n=6), APR 20mg twice daily (n=11), APR 30mg twice daily (n=26) and APR 40mg once daily (n=2) treatment arms as well as a single event in the APR 10mg twice daily group. The EAIR per 100 PY for malignancy (overall, and by subtype [skin versus solid organ]) were similar between the treatment arms.

Non-melanoma skin cancers (squamous cell/basal cell) accounted for 30 of the 46 adjudicated malignancies – equally distributed among the treatment groups for both indications. Of the solid cancers, there were 4 cases of prostatic adenocarcinoma, 2 cases of breast cancer (both ductal carcinomas), 2 cases of lung cancer (1 case each of small cell and bronchioloalveolar carcinomas); and 1 case each of B-cell lymphoma, neoplasia of the oral cavity and mesothelioma. The time from initiation of APR therapy to the onset of malignancy varied between 36 to 440 days with no clear temporal or dose-response relationship between dosing and the onset of the event. Several of the subjects had a medical history that increased their risk of malignancy including a family history of associated cancer or tobacco use.

8.4.3.2. Other studies

One patient in Study PSOR-004 [information redacted]had an unwitnessed death on study day 140. The subject was randomized initially to APR 20mg twice daily but increased the dose to 30mg twice daily 55 days prior to death. The subject had a past history of cardiac arrhythmia treated with ablation. The investigator reported the death as being due to myocardial infarction complicated by arrhythmia. A 63 year old man in Study PSOR-005 was found dead in his closed garage with a motorcycle running on study day 84. He was randomised to PBO treatment. An additional death was reported in a study enrolling subjects with RA. The patient died of acute myeloid leukaemia (AML). The AML was diagnosed nearly 12 months after completing a 3-week course of APR 30mg twice daily. Given the short-term exposure to APR and the temporal relationship of the diagnosis of AML, a casual relationship for APR does not appear to be likely.

A total of 15 SAEs have been reported in the supporting studies, including 3 SAEs recorded in Study PSA-005. SAEs reported from the Behçet's disease study (n=6), asthma trial (n=3) and the clinical pharmacology studies (n=1; exacerbation of COPD) were considered unrelated to APR treatment except for a single case of influenza in Study BCT-001. There was 1 case of depression with aggression in Study ASTH-001 but this was considered to be unrelated to APR.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

8.4.4.1.1. Phase 3 PsA studies

The overall incidence of AEs in the Phase 3 PsA dataset leading to treatment discontinuation between weeks 0-16 was higher in APR treated subjects (4.4% [30/676] in the APR 20mg twice daily group and 5.7% [38/672] in the APR 30mg twice daily arm) compared to PBO subjects (3.6%; 24/671). The most frequently reported AEs leading to drug withdrawal in APR treated subjects were nausea (1.6-1.9%), diarrhoea (1.5-1.9%), headache (1.0-1.6%); and vomiting, fatigue and dizziness (all affected 0.4% of patients in each APR treatment group). The above types of AEs occurred at a slightly higher incidence in the APR 30mg twice daily group.

For weeks 0-24 and weeks 0-52, the number of subjects with AEs leading to drug withdrawal was similar between the APR 20mg and APR 30mg treatment arms, and appeared to occur at a slightly lower overall frequency after 16 weeks. The data demonstrates that the greatest proportion of AEs leading to drug withdrawal occurred during weeks 0-16 weeks of treatment.

The overall incidence of AEs in the Phase 3 PsA dataset leading to treatment discontinuation during the APR-exposure period was 6.9% (67/972) in the APR 20mg twice daily group and 7.5% (73/973) in the APR 30mg twice daily arm. The most frequently reported AEs leading to drug withdrawal during the APR-exposure period of the PsA Phase 3 studies were similar to those observed in the PBO-controlled period, namely, nausea (1.0-2.0%), diarrhoea (1.2-2.1%), headache (0.5-1.4%) and vomiting (0.2-0.8%), all of which appeared to increase in a dose-dependant manner.

8.4.4.1.2. Phase 3 PSOR studies

The overall incidence of AEs in the Phase 3 PSOR dataset leading to treatment discontinuation between weeks 0-16 was higher in APR 30mg twice daily group (5.4%; 45/832) compared to PBO arm (3.8%; 16/418). The most frequently reported AEs leading to drug withdrawal, which occurred at a higher frequency in the APR treated subjects, were nausea (1.6 versus 0.2%), diarrhoea (1.0% versus 0.2%), headache (0.6% versus 0) and dyspepsia (0.4% versus 0). Patients in the PBO group had a higher frequency of withdrawal due to PSOR (1.0% versus 0.5%).

For weeks 0-52, the incidence of subjects withdrawing due to AEs remained constant or less over time compared to that observed during the first 16 weeks of APR treatment. The overall incidence of AEs in the Phase 3 PSOR dataset leading to treatment discontinuation during the APR-exposure period was 8.4% (99/1184) for those receiving APR 30mg twice daily. The most frequently reported AEs leading to drug withdrawal during the APR-exposure period of the PSOR Phase 3 studies were similar to those observed in the PBO-controlled period, namely, nausea (1.4%), diarrhoea (0.9%) and PSOR (0.9%).

8.4.4.2. Other studies

Similar results to those observed in the Phase 3 PsA and PSOR studies were also reported during the Phase 2 trials in PsA and PSOR, as well as the studies in Behçet's disease, RA and asthma plus the clinical pharmacology studies. AEs leading to drug interruption or withdrawal from these studies mirrored the frequency and types of AEs leading to drug withdrawal outlined above. A total of 5 subjects (1.1% of 436; 3 received APR 30mg twice daily, and 1 each received APR 60mg and 80mg daily) withdrew due to AEs in the clinical pharmacology studies. The most

common AEs in the supporting studies resulting in drug cessation or interruption were diarrhoea, nausea, vomiting and headache.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

8.5.1.1.1. Phase 3 PsA studies

Assessment of liver function tests (LFTs) demonstrated that 2 PBO-treated subjects (0.2%), 2 patients in the APR 20mg group (0.2%), and 7 subjects in the APR 30mg cohort (0.6%) had recorded serum ALT or AST values >3 x ULN during the PBO-controlled period. Additionally, 2 subjects in each of the APR treatment groups had serum bilirubin values >1.8 x ULN.

Given the increased frequency of gastrointestinal AEs, LFTs were analysed intensely by the sponsor. No cases of abnormal LFTs met Hy's Law criterion. More than 80% of subjects had normal (≤1 x ULN) ALT and AST values during 52 weeks of follow-up in the Phase 3 PsA studies. The majority of the subjects reporting LFTs >3 x ULN (20 APR treated subjects in total by week 52) had these elevations only once with resolution of the abnormality while remaining on APR. None of the subjects had an AST/ALT value >3 x ULN with an associated increase in bilirubin >1.5 x ULN. A single subject from the APR 30mg group reported an increase of ALT (1.3 x ULN) and AST (1.1 x ULN) in conjunction with an elevated bilirubin (>1.5 x ULN). This subject had a medical history significant for several years of hyperbilirubinemia. Many of the subjects were receiving concomitant medications known to be hepatotoxic (including MTX or statin drugs) as well as having underlying predisposing conditions (such as obesity, type 2 diabetes and/or alcohol consumption). Abnormal liver function tests occurred at various times ranging from study day 24 to 288. No abnormalities of LFTs resulted in treatment discontinuation.

8.5.1.1.2. Phase 3 PSOR studies

Between baseline and week 16 in the Phase 3 PSOR dataset, elevated serum transaminases >2-3 x ULN were recorded in 0.5% of the PBO treated subjects and 0.6% of APR 30mg twice daily patients. Additionally, 0.2% of subjects in the PBO and APR treatment groups had serum bilirubin values >1.8 x ULN.

In the APR-exposure period, a total of 20 APR treated subjects developed abnormal LFTs after commencing treatment: 18 involved ALT and/or AST ≥3 x ULN (all without raised serum bilirubin) and 2 subjects developed isolated increases in serum bilirubin ≥1.8 x ULN. For 16 of the 18 patients with raised serum transaminases, an underlying co-factor for abnormal LFTs was present (e.g. obesity with fatty liver disease, type 2 diabetes, alcohol consumption and/or hyperlipidaemia). The 2 cases of hyperbilirubinaemia occurred in patients without risk factors for liver disease. The subjects were asymptomatic and the elevated results lasted between 16 and 35 days. Abnormal liver function tests occurred at various times ranging from study day 13 to 461. No abnormalities of LFTs resulted in treatment discontinuation.

8.5.1.2. Other studies

In the clinical pharmacology studies (pooled dataset), a total of 4 subjects (0.9%) recorded abnormal LFTs (all raised serum transaminases). There were no other significant abnormalities of LFTs in the supporting studies.

8.5.2. Kidney function

8.5.2.1. Pivotal studies

Analysis of renal function over time, by individual subject changes, and individual clinically significant abnormalities were similar in the APR treatment groups to that observed in the PBO arm during the PBO-controlled periods and did not change with time in the APR-exposure

periods in either the Phase 3 PsA or PSOR datasets. Marked abnormalities of renal function (defined as blood urea nitrogen >15 mmol/L or serum creatinine >1.7 x ULN) were rare (≤0.1% incidence), and not treatment or dose related to APR.

8.5.2.2. Other studies

No significant changes in renal function were noted in the supporting studies.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

In the Phase 3 studies, the most frequent markedly abnormal clinical chemistry values reported during the PBO-controlled periods included elevated triglycerides (>3.4 mmol/L) and uric acid levels (>590 µmol/L [male] or >480 µmol/L [female]) in the PBO (10% and 3% respectively), APR 20mg (9% and 3%, respectively), and APR 30mg (9% and 3%, respectively) treatment arms. Except for elevated serum phosphate, all marked abnormalities in clinical chemistry values occurred in similar proportions of subjects in all treatment arms and no dose-response relationship for APR was noted. Similar results were observed during the APR-exposure period.

In the Phase 3 PsA studies, a greater proportion of APR 30mg twice daily treated subjects were noted to have elevated phosphate levels >1.60 mmol/L compared with subjects in the PBO and APR 20mg twice daily groups during the PBO-controlled (1.3%, 1.8% and 2.5%, respectively). In the APR-exposure period, hyperphosphatemia was recorded in 3.6% of patient receiving APR 20mg twice daily and 4.7% of subjects taking APR 30mg twice daily. Phosphate levels were also slightly higher in the APR treated subjects versus PBO in the Phase 3 PSOR dataset, albeit to a lesser degree. There were no correlative changes regarding other electrolytes or associated AEs from either dataset (PsA or PSOR). The clinical significance of this finding is unclear.

8.5.3.2. Other studies

No significant changes in clinical chemistry (excluding liver function tests) were noted in the supporting studies.

8.5.4. Haematology

8.5.4.1. Pivotal studies

8.5.4.1.1. Phase 3 PsA studies

The most frequently abnormal haematology value reported during the PBO-controlled phases of the Phase 3 PsA studies were decreased lymphocyte counts, which occurred in 0.5% of PBO (3/589) and APR 30mg twice daily (3/589) treated subjects. One case of neutropenia was recorded in each of the 3 treatment arms (0.2% incidence) in the first 16 weeks of treatment follow-up. For the APR-exposure period, the incidence of lymphopenia was 1.5% in both the APR 20mg and APR 30mg twice daily patient groups.

8.5.4.1.2. Phase 3 PSOR studies

Between weeks 0 and 16 in the Phase 3 PSOR studies, the most common abnormal haematology result was lymphopenia which affected 3 subjects each in the PBO (0.9% of 348) and APR 30mg twice daily groups (0.4% of 764). No cases of neutropenia or thrombocytopenia were recorded. In the APR-exposure period, 1.2% (13/1069) of subjects recorded lymphopenia.

8.5.4.2. Other studies

No clinically significant abnormalities of haematology values were observed in the supporting studies apart from 2 cases of mild leucopenia and 1 case of mild thrombocytopenia in the clinical pharmacology trials. Overall changes in haematology values were small, typically well balanced between treatment arms and not correlated with clinically meaningful AEs.

8.5.5. Electrocardiograph

8.5.5.1. Pivotal studies

In the Phase 3 PsA dataset, 8 subjects (5 treated with APR 20mg twice daily and 3 treated with APR 30mg twice daily) had an AE of prolonged QT interval on ECG. In addition, 1 subject each in the APR 30mg twice daily cohort experienced an AE of shortened PR interval, shortened QT interval, abnormal T-wave and non-specific repolarization abnormality on ECG.

In the Phase 3 PSOR dataset, 3 subjects (all treated with APR 30mg twice daily) had AEs related to ECG changes: 1 subject each with QT interval, abnormal T-wave (associated palpitations), non-specific abnormal ECG.

8.5.5.2. Other studies

Study PK-008 was a specific QT interval trial that examined the relationship between APR and significant ECG changes. This has been evaluated in the PD section of this report. No subjects in the other supporting studies were reported to have significant abnormalities on ECG.

8.5.6. Vital signs

8.5.6.1. Pivotal studies

During the PBO-controlled periods of the Phase 3 PsA trials, the mean change from baseline to week 16 ranged among the 3 treatment groups (PBO, APR20mg and APR 30mg) between -0.2 to -1.1 mmHg for systolic BP and between -0.1 to -1.0 mmHg for diastolic BP. During the APR-exposure period, the mean change from baseline to the end of the follow-up period ranged between the 2 APR treatment groups between -0.9 to -1.1 mmHg for systolic BP and was -1.3 mmHg for diastolic BP. Mean changes from baseline for all vital signs parameters were generally consistent across treatment groups, and no dose relationship with APR was noted. The overall mean changes from baseline to the end of treatment in pulse rate was <1 beat per minute in the PBO, APR 20mg and APR 30mg treatment arms. Similar observations were noted when changes from baseline over time in vital signs were analysed for the Phase 3 PSOR studies.

8.5.6.2. Other studies

No clinically relevant changes in vital signs were noted in any of the supporting studies.

8.5.7. Changes in body weight

8.5.7.1. Pivotal studies

In the Phase 3 PsA studies, the mean change in weight from baseline to week 52 was -1.25 kg for patients receiving APR 20mg twice daily and -1.68 kg for subjects given APR 30mg twice daily. Weight decrease was also reported for roflumilast (another PDE4 inhibitor) in clinical studies. The COPD population studied with roflumilast had a lower mean BMI (approximately 26 kg/m^2) than those involved in the PsA trials (mean BMI of 30.3 kg/m^2). The mean change in weight with roflumilast was -2.0 kg over the first year of treatment. In the Phase 3 PSOR studies, the mean change in weight from baseline to week 52 was -1.99 kg for patients receiving APR 30mg twice daily.

8.5.7.2. Other studies

No significant weight changes were reported in the supporting studies for either indication, but many of the trials were of insufficient duration to examine this variable.

8.6. Post marketing experience

Not applicable as APR at the time of this submission had not received registration anywhere in the world for the treatment of PsA or PSOR.

8.7. Safety issues with potential for major regulatory impact

8.7.1. Psychiatric disorders

In the Phase 3 PsA trials, treatment with APR was associated with increased rates of reported AEs of depression. Between weeks 0 and 16 (PBO controlled periods), 1.0% (10/998) of patients treated with APR reported depression or depressed mood compared with 0.8% (4/495) treated with PBO. Furthermore, during the clinical trials, 0.3% (4/1441) of patients treated with APR discontinued due to depression or depressed mood versus no PBO treated subjects (0/495). Between weeks 0 and 16 in the Phase 3 PsA studies, serious depression was recorded in 2/1945 (0.1%) of patients treated with APR (1 subject receiving 20mg twice daily and the other subject was treated with 30mg twice daily), and serious anxiety in 1/1945 (0.1%). No PBO treated subject experienced serious depression or anxiety. The event rate for depression and anxiety did not increase over time with continued APR therapy. In the Phase 3 PSOR studies, only 1 patient (0.1% of 1184) developed serious depression. The patient withdrew from the trial because of this AE.

In the total APR dataset (including all Phase 2 and 3 studies), 7 patients have experienced serious self-injury (2 had suicidal ideation, 3 attempted suicide, and 2 had a completed suicide).[5] In these 5 cases, 3 received treatment with APR 30mg twice daily, 2 took APR 20mg twice daily and 1 subject was receiving PBO. Based on epidemiological data, the incidence of suicidal ideation and attempt lies within the expected range for matched subjects.

8.7.2. Weight loss

Between weeks 0 and 16 in the Phase 3 PsA studies, weight loss of 5-10% was recorded in 35/972 (4.0%) of patients treated with APR 20mg twice daily and 35/973 (4.1%) of subjects treated with APR 30mg twice daily. Weight loss >10% was experienced by 6 (0.7%) and 7 (0.8%) of patients in the APR 20mg twice daily and APR 30mg twice daily groups, respectively. In the APR exposure period, weight loss of 5-10% was recorded in 98/972 (10.4%) of patients receiving APR 20mg twice daily and 120/973 (12.7%) of patients taking APR 30mg twice daily. Weight loss >10% was experienced by 42 (4.5%) and 36 (3.8%) of patients in the APR 20mg twice daily and APR 30mg twice daily groups, respectively.

In the Phase 3 PSOR studies, a total of 132/1184 (11.7%) of patients treated with APR recorded weight loss of 5-10% between weeks 0 and 16, and 22 (0.2%) of subjects experienced >10% weight reduction. In the APR exposure period, a total of 162 subjects (14.3% of 1184) recorded weight loss of 5-10% and 65 (5.7%) recorded >10% weight loss.

8.7.3. Hypersensitivity reactions

Between weeks 0 and 16 in the Phase 3 PsA studies, hypersensitivity reactions were reported for 3/1945 (0.2%) of APR treated subjects and no PBO patients. In the APR exposure period, hypersensitivity was recorded in 4/1945 (0.4%) of patients receiving APR. One patient who took APR 40mg once daily in Study PSA-001 discontinued due to recurrent hypersensitivity reactions. The first reaction occurred on study day 27 and involved throat tightness, pruritus and urticaria. This AE resolved within 2 days but recurred twice upon rechallenge with APR.

In the Phase 3 PSOR studies, a total of 4/1184 (0.3%) of patients treated with APR 30mg twice daily reported hypersensitivity AEs between weeks 0 and 16. In the APR exposure period, a total of 8 subjects (0.7% of 1184) reported hypersensitivity reactions, including 1 case of anaphylaxis in patient taking APR 10mg twice daily (study day 136).

8.7.4. Unwanted immunological events

APR is not a biologic DMARD and the issue of anti-drug antibodies is not applicable to this drug.

[5] One subject completed suicide, while a second subject was considered as a completed suicide by the FDA. Both subjects were on placebo.

PDE4-inhibitors, including APR, have been demonstrated to induce inflammatory perivascular changes on histopathology consistent with vasculitis in animal studies. Consequently, investigators were instructed to monitor for any clinical signs and symptoms of vasculitis during the APR clinical program. No patients in the Phase 3 studies (PsA or PSOR) were identified as experiencing vasculitis. Two subjects involved in a RA trial were reported to have vasculitis. However, 1 of those subjects (given APR 30mg twice daily) was diagnosed with rheumatoid vasculitis, which resulted in discontinuation from the study. The second subject with RA (randomized to PBO) was diagnosed with cutaneous vasculitis, which subsequently resolved. As vasculitis is known to occur in patients with RA, the data does not support an association between APR and vasculitis.

8.8. Other safety issues

8.8.1. Safety in special populations

Pregnant and lactating women were excluded from the studies throughout the clinical development program. However, as of 15 May 2013, a total of 21 pregnancies (7 female subjects and 14 partners of male subjects) have been recorded in the APR studies. Of the 7 female subjects, 5 occurred while taking APR. The other 2 female subjects either received PBO or became pregnant during the pre-treatment period. Two of APR exposed female subjects elected to have a termination of pregnancy, while another 2 women had full term, live births of healthy infants. One pregnancy was ongoing at the time of data cut-off. In the 14 male partner pregnancies, 11 occurred in subjects actually taking APR. No congenital abnormalities have been reported in the 5 completed births.

In both the Phase 3 PsA and PSOR studies, subjects were required to have a normal serum creatinine value ($\leq$1.5mg/dL) at baseline. However, based on CrCL a total of 313 subjects in the PsA studies (102 in the PBO group, 106 in the APR 20mg arm and 105 in the APR 30mg group) had a CrCL of <90 mL/min at baseline, including 34 subjects with CrCL of 30-60 mL/min (10 in each APR treatment group and 14 in the PBO arm). In the Phase 3 PSOR trials, a total of 119 subjects (29 in the PBO group and 89 in the APR 30mg twice daily arm) had a CrCL of <90 mL/min at baseline, including 12 subjects with CrCL of 30-60 mL/min (9 in the APR treatment group and 3 in the PBO arm). The safety profile (incidence and type of AEs) recorded in patients with mild renal impairment was consistent with that observed in subjects with normal renal function.

8.8.2. Safety related to drug-drug interactions and other interactions

In the Phase 3 PsA studies, drug-drug interactions were assessed by baseline DMARD use (conventional and biologic); baseline and concurrent MTX, LEF and SSZ use; and baseline and concomitant oral CS use. In the Phase 3 PSOR trials, drug-drug interactions were assessed by prior biologic use, baseline DMARD use and previous phototherapy. In addition, in both treatment indications, the concomitant use of common medicines including lipid lowering drugs, analgesics, diabetic medicines, calcium channel blockers, diuretics and medicines for acid related disorders were assessed for AEs. No new safety signal was observed in the above analyses.

8.9. Evaluator's overall conclusions on clinical safety

A total of 2401 subjects have received APR in Phase 2 and 3 clinical studies for the treatment of PsA, PSOR and RA in doses ranging from 10mg twice daily to 30mg twice daily. A total of 672 subjects in the overall APR exposure dataset have received APR 30mg twice daily (the proposed registration dose) for at least 24 weeks, and 269 subjects have received APR 30mg twice daily for at least 48 weeks. Overall, there is a sufficient volume of data to make a meaningful

assessment of APR safety for up to 52 weeks of treatment in the newly proposed treatment indications of active PsA and PSOR.

In general, the study populations had baseline characteristics (demographic, disease-related and co-morbidity) indicative of the intended target population for the claimed indications. The studies enrolled almost equal proportions of male and female subjects who were mainly Caucasian (>90%) and middle aged (median age of 51 years). However, the pivotal studies excluded patients with a high baseline risk of infection. In addition, there is no or very limited experience in certain patient subgroups of relevance including subjects with renal or hepatic impairment, pregnant or lactating women, and those with a low body weight (<50 kg).

The overall frequency of all AEs were higher in the APR treatment groups versus PBO, and generally had a slightly higher incidence in the APR 30mg twice daily groups compared with APR 20mg twice daily treatment arms. The most frequently reported AEs were gastrointestinal disorders (mainly, diarrhoea and nausea) and headache, both of which occurred at a higher frequency in the APR treatment groups in a dose-dependant manner. The majority (>95%) of AEs were reported as mild to moderate in severity. The highest incidence of diarrhoea, nausea and headache events occurred with the first 14 days of initiating APR therapy and reduced after 30 days. Upper respiratory tract infections were also reported in >5% of subjects and occurred more frequently in subjects receiving APR than in those receiving PBO. Most of these infections were mild to moderate in severity, and self-limiting. No SAEs due to URTI were reported. Diarrhoea, nausea, headache, URTI, vomiting and dyspepsia are included in the PI as potential adverse drug reactions. In the Phase 3 studies for both indications, serious adverse events occurred in approximately equal frequencies between PBO and APR treated subjects. Safety analyses did not suggest a clinically important difference in the type of SAEs between APR treated subjects and those treated with PBO.

A total of 7 deaths have been reported in the broader APR development program with 1 death occurring in the PsA studies (subject received APR 20mg twice daily), 5 deaths were reported during the PSOR studies (2 given PBO, 2 received APR, and 1 initially received APR but then was re-randomised to PBO during the randomized withdrawal phase) and 1 additional death possibly related to APR therapy occurred in patient with RA. Two of the deaths were apparent suicides,[6] which is concerning since the PDE4-inhibitor roflumilast has a warning included in its PI about the potential for increased psychiatric events, including depression and suicidal behaviour. A review of the psychiatric AEs in the APR program has been performed. Review of the data concluded that the current data submitted in this application does not suggest an increased risk of suicidal behaviour in patients treated with APR. However, in the Phase 3 PsA studies patients treated with APR were observed to have a slightly higher incidence of depression or depressed mood, and discontinuations due to these AEs compared to PBO treated subjects.

A treatment-dependant decrease in body weight was observed in the PsA and PSOR studies. A greater proportion of APR-treated subjects experienced a >5% weight loss compared to PBO-treated subjects. No subject had a weight decrease of >20% and 1 subject discontinued due to weight decrease during the APR exposure period. The potential for significant weight loss is included in the PI and is an issue requiring ongoing pharmacovigilance. Analyses of adjudicated events for serious infections, major adverse cardiovascular events and malignancies did not indicate any imbalance between APR and PBO treated subjects. Additional analyses evaluating the incidence of tuberculosis, psychiatric events and vasculitis were performed and no safety signal with APR therapy was identified.

Markedly abnormal laboratory test results were infrequent and transient. In general, analyses of mild and moderate laboratory abnormalities did not show an increased risk between either

[6] One subject completed suicide, while a second subject was considered as a completed suicide by the FDA. Both subjects were on placebo.

APR 20 mg twice daily or APR 30mg twice daily treatment groups. The vast majority of laboratory abnormalities was transient and did not lead to study drug discontinuation. No cases of hepatic failure, or LFT elevations meeting Hy's Law criteria, were reported. Myelosuppression was not observed based on routine laboratory testing.

APR has demonstrated an acceptable safety profile when used alone or in combination with DMARD therapy including MTX, SSZ and LEF.

In summary, the data submitted in this submission is sufficient to assess the overall safety of APR in adult patients with active PsA and/or PSOR. The most commonly occurring AEs associated with APR were diarrhoea, nausea, vomiting, headache and URTI. These AEs typically occurred in the first 14 days after starting APR, were usually mild or moderate in severity, and generally resolved within 30 days while subjects continued receiving APR. Treatment with APR was also associated with weight loss, with approximately 10% of APR treated subjects losing between 5%-10% of their body weight over 52 weeks. Except for the AEs of diarrhoea, nausea, vomiting, headache and URTI, no imbalance was observed for adverse events of special interest including adjudicated events of serious infections, major adverse cardiovascular events and malignancies. However, there is limited long-term safety data in the current submission (beyond 52 weeks of treatment follow-up) to assess the risk of some types of AEs such as malignancy and adverse cardiovascular events, which will require much greater durations of follow-up.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of APR in the proposed usage are:

- Clinically meaningful improvements in the signs and symptoms of PsA (that is, ACR response criteria), as well as physical functioning (i.e. change from baseline in HAQ-DI score) when given to patients with active established PsA, many of whom have failed to respond to conventional treatment (DMARD [mainly MTX] and NSAID).
- Clinically meaningful improvements in the signs and symptoms of PSOR (that is, PASI score changes), as well as health related QOL (for example, DLQI scores) when given to patients with moderately to severely active PSOR who are candidates for systemic or phototherapy.
- Provides an alternative therapy (different mechanism of action) to current drugs in patients with active PsA or PSOR who have failed to respond to conventional treatment.
- Convenient dosing schedule (every 12 h) using a convenient mode of administration (oral therapy).

9.2. First round assessment of risks

The risks of APR in the proposed usage are:

- Higher incidence of gastrointestinal adverse events such as nausea, vomiting and diarrhoea, which increase in a dose dependent manner with APR. These were a common cause of drug discontinuation and typically occurred in the first 14 days after starting treatment.
- APR is associated with weight loss in a dose independent manner with approximately 10% of patients losing between 5-10% of their baseline body weight.
- Slightly increased incidence of depression or depressed mood compared to PBO treated subjects, which may result in treatment discontinuations.

- Possible signal of adverse effects on liver function tests with a higher frequency of APR treated subjects developing increases in serum transaminases compared with PBO.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of APR for up to 52 weeks of treatment follow-up in the target populations of adult subjects with active PsA and PSOR is favourable.

9.3.1. PsA indication

The overall benefit-risk assessment supports approval of APR for the treatment of active PsA in adult patients. The submitted data demonstrated consistent efficacy in favour of APR versus PBO in PsA. Of the 2 APR doses examined, the 30 mg twice daily regimen provided higher numerical responses compared with the 20 mg twice daily posology. The overall magnitude of the treatment effect size was modest compared to biologic therapies. The major safety findings identified in the program were gastrointestinal AEs and weight loss. Given the nature of the safety findings and the lack of a clear dose related AE profile (apart from gastrointestinal AEs), the 30 mg twice daily dose of APR is acceptable as the proposed dose regimen. Appropriately, the registration proposes an upward titration of APR during the first week of treatment, which was undertaken during the Phase III studies and appears to lessen the incidence of gastrointestinal AEs.

9.3.2. PSOR indication

The overall benefit-risk assessment supports approval of APR for the treatment of active PSOR in adult patients. The submitted data demonstrated consistent efficacy in a dose related manner for APR versus PBO. The overall magnitude of the treatment effect size was similar to other conventional systemic therapies. The major safety findings (type and incidence) recorded in patients with PSOR were similar to that observed in PsA subjects (mainly, gastrointestinal AEs and weight loss).

10. First round recommendation regarding authorisation

10.1. PsA Indication

The evaluator recommends acceptance of the sponsor's proposed registration of APR for the treatment indication of active PsA in adult patients. Approximately half of all subjects in the Phase III PsA studies took MTX concurrently with APR, and the beneficial clinical responses in those not taking concomitant DMARD (usually MTX) were similar. The sponsor has not proposed in the treatment indication the use of APR in patients with PsA with or without DMARD, but nonetheless has justified that scenario. Furthermore, most of the Phase III studies recruited subjects with active PsA who had failed to adequately respond to conventional treatment (DMARD [mainly MTX] and/or NSAID), but did include a subset of patients with prior biologic therapy exposure (mainly, anti TNF medicines). Regarding posology, efficacy results from the Phase III program generally supported a greater numerical advantage for the APR 30 mg twice daily regimen compared to the APR 20 mg twice daily posology, but there were limited statistically significant analyses to support the conclusion that APR 30 mg twice daily was superior to APR 20 mg twice daily. Apart from gastrointestinal AEs (usually of mild-moderate severity and seen at the commencement of therapy), safety was similar in both APR treatment regimens. As such, the evaluator recommends acceptance of the sponsor's proposed registration of the 30 mg twice daily regimen for adult patients with active PsA.

10.2. PSOR Indication

The evaluator also recommends acceptance of the sponsor's proposed registration of APR for the treatment indication of active PSOR in adult patients. The proposed wording of treatment indication in patients with PSOR has an additional element relating to potential patients being candidates for systemic or phototherapy. The current submission provides robust evidence of improving the symptoms and signs of active PSOR, as well as health related QOL. Regarding posology in PSOR, only the 30 mg twice daily dose of APR was investigated in the Phase III program. In addition, the dose finding trial (Study PSOR-005) demonstrated a clear dose response relationship for APR, which supported the advantage of the 30 mg twice daily regimen compared to the APR 20 mg twice daily dose in treating adult patients with active PSOR.

10.3. Both indications

Should approval of the sponsor's proposed registration of treatment indications be granted, the evaluator also recommends that approval be subject to:

- Satisfactory response to the questions below;
- Regular periodic safety update reports; and
- When available, the sponsor provides the TGA with the final clinical study reports for the extension phases of each study, as well as the Week 52 report for Study PSA-005.

11. Clinical questions

11.1. Pharmacokinetics

- APR is primarily eliminated as metabolites formed by cytochrome P450 (CYP) mediated oxidative metabolism via CYP3A4, 1A2 and 2A6 enzymes. Could the sponsor comment on whether there has been any evaluation of the consequences of genetic polymorphism in these CYP enzymes, and if not, are there any potential clinical consequences?
- None of the clinical pharmacology studies in this submission appear to have evaluated the effect of administration timing on the bioavailability and pharmacokinetic parameters of APR. Could the sponsor comment on whether diurnal variation in APR pharmacokinetic parameters has been examined and any potential impact?
- Could the sponsor provide a summary assessment of the intra-subject and inter-subject variability for the pharmacokinetics of APR, and comment on whether or not such variability may be clinically relevant?
- Could the sponsor justify how the pre specified, clinically relevant 90% CI bioequivalence margin of 50% to 200% for pharmacokinetic parameters in Study CP-025 was determined as this appears to be overly generous?

11.2. Pharmacodynamics

Nil

11.3. Efficacy

- Subjects with a body weight of ≥ 100 kg appear to have a higher clearance and larger volume of distribution for APR, and the clinical pharmacology studies suggested that this may not be of clinical significance. However, in the subgroup analyses of Study PSA-005 for

the primary efficacy endpoint, APR did not appear to result in a significant treatment related effect for patients weighing ≥ 100 kg. Could the sponsor comment on the impact of subject obesity upon clinical efficacy with APR?

- In Study PSOR-005, the majority of subjects who entered the first extension phase completed follow-up to Week 52 (74.6%; 156/209). However, only a small number of patients (n = 33) entered the long term extension phase (beyond Week 52), 28 of which are still continuing at Week 88. Could the sponsor comment as to why participating patient numbers decreased significantly after Week 52. Was the reduced participation beyond 52 weeks due to waning efficacy, adverse events or some other reason?

11.4. Safety

- As APR is known to affect various cytokines in the inflammatory response, has the sponsor performed any vaccine sub-studies in patients with PsA or PSOR to determine the effect of Otezla on protective immune status?
- For the adjudicated safety concerns of special interest (MACE, serious infection and malignancy) in the completed Phase II and III studies (for any treatment indication), could the sponsor provide the relative risks and upper limit of the 95% confidence limit for relative risk, in addition to the point estimates (EAIR) which have currently been provided for APR versus PBO?

12. Population pharmacokinetics

Table 21 shows studies providing pharmacokinetic/pharmacodynamic (PK/PD) data.

Table 21: Studies providing PK/PD data.

Population PKPD Study	Studies contributing Data	Study Population	Number of Subjects
Study PSA-001-PK	Study PSA-001	Psoriatic arthritis	34 popPK 199 total
Study PSA-002-PK	Study CC-10004-PSA-002	Psoriatic arthritis	34
	Study PSA-001-PK	Psoriatic arthritis	34 popPK
	Study CC-10004-BA-001	Healthy male volunteer	12
	Study CC-10004-BA-002	Healthy volunteer	16
	Study CC-10004-PK-008	Healthy volunteer	56
	Study CC-10004-PK-010	Healthy volunteer	14
Study PSOR-005-PK	Study PSOR-005-PK	Moderate-to-Severe Plaque-Type Psoriasis	68
Study PSOR-008-PK	CC-10004-PSOR-008	Moderate-to-Severe Plaque-Type Psoriasis	166
	CC-10004-PSOR-005	Moderate-to-Severe Plaque-Type Psoriasis	68
	CC-10004-BA-001	Healthy male volunteer	12
	CC-10004-BA-002	Healthy volunteer	16
	CC-10004-PK-008	Healthy volunteer	56
	CC-10004-PK-010	Healthy volunteer	14
	CC-10004-CP-022	Healthy volunteer	46
	CC-10004-CP-024	Healthy volunteer	36
Study RA-002-PK	Study CC-10004-RA-002	Rheumatoid Arthritis	75
	CC-10004-BA-001	Healthy male volunteer	12
	CC-10004-BA-002	Healthy volunteer	16
	CC-10004-PK-008	Healthy volunteer	56
	CC-10004-PK-010	Healthy volunteer	14

12.1. Description of PK and PK/PD studies

12.1.1. Study PSA-001

12.1.1.1. Objective of the analysis

- To estimate the systemic exposure of 20 mg, oral administration twice daily and 40 mg once daily of apremilast in subjects with active psoriatic arthritis
- To explore the relationship between 20 mg, oral administration twice daily and 40 mg once daily of apremilast and PD activity, as well as safety measurements in subjects with active psoriatic arthritis

12.1.1.2. Data

The data were obtained from a single phase 2 study conducted in a population of subjects with a minimum of 6 months history of psoriatic arthritis. Subjects were randomised 1:1:1 to apremilast 20 mg, twice daily, apremilast 40 mg once daily or placebo. For both active treatment panels the dosing commenced with apremilast 10 mg once daily for three days, then 20mg once daily for 3 days, followed by the allocated treatment. The treatment phase was for 12 weeks. The study had a 12 week extension phase, for which the subjects in the placebo arm were randomised to one of the active treatment arms.

There were 204 subjects enrolled in the study: 69 in the 20 mg twice daily group, 67 in the 40 mg once daily and 68 in the placebo. Twenty two were included in the non-compartmental analysis: 12 in the 20 mg twice daily group and ten in the 40 mg once daily. Thirty three were included in the population pharmacokinetic analysis: 18 in the 20 mg twice daily group and 15 in the 40 mg once daily. There were 199 subjects in the PKPD/safety analysis: 65 in the 20 mg twice daily, 66 in the 40 mg once daily and 68 in the placebo.

There were 498 samples available for the population PK analysis. Of these 36 were BLQ and were excluded, 27 were deemed to be outliers and were excluded and all data from one subject (deemed to be non-adherent) were excluded. The analysis used 418 plasma concentration observations. Of the 34 subjects entered into the population PK analysis, there were 17 (50%) females, 17 (50%) males, and the mean (SD) age was 52.6 (11.48) years.

12.1.1.3. Methods

The analysis was approached by first performing a non-compartmental PK analysis using WinNonlin Version 5.2 (model 200) on the Day 71 and Day 85 data. The following parameters were calculated: AUC0-8, Cmin, Cmax, and Tmax. A subsequent population PK analysis was performed using NONMEM Version VI (Level 1.1) with the first-order conditional estimation ("FOCE") and the INTERACTION option. The PD analysis was performed by logistic regression, using the PK parameters derived from the first two steps as the exposure variables and the PD measures as the outcome variables. The logistic regression analysis was performed using R® Version 2.9.2. Receiver operating characteristic (ROC) curves were used to detect the exposure marker that best predicted the clinical response profile of apremilast.

Plasma apremilast was measured using validated chiral liquid chromatography-mass spectrometry methods (LC-MS/MS). The lower limit of quantitation (LLOQ) was 1.00 ng/mL in plasma for apremilast. Concentration values of plasma apremilast that were reported as below the limit of quantification (BLQ) were set to zero for non-compartmental PK. Population PK and statistical analyses.

The covariates explored were: age, sex, body weight, BMI, CRCL (estimated using the Cockcroft-Gault equation), MTX comedication, CYP3A, CYP1A2 and CYP2A6 substrate co-administration and smoking status. Continuous covariates were introduced in the structural model using a power function. Categorical covariates were introduced in the structural model using a linear model.

The model diagnostics were:

- Nonparametric bootstrap resampling approach
- Plots: DV vs PRED, DV vs IPRED, plots of CWRES, Scatter plot matrix of ETAs versus continuous covariates, box plots of ETAs versus categorical covariates, complete individual plots.

The PKPD analysis used the posthoc estimates from the model of AUC0-24, Cmax and Cmin for 199 study subjects, many of whom did not have any PK observations. Hence these estimates were based on the final model, and used each subject's covariates to estimate their PK parameters.

The PD outcome measures were:

- Individual clinical response data (ACR20, ACR50, ACR70, ACR90, PsARC, and DAS28). It was intended to explore these associations using an E_{max} model.
- Immunohistochemistry/molecular markers for skin and synovial biopsies:
  - Quantitation of T (CD3, CD4, CD8, Granzyme B) and B lymphocytes (CD20); macrophages (CD68, CD163); and synoviocytes (CD55)
  - Adhesion markers: intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin ligand adhesion molecule 1 (ELAM-1)
  - Angiogenesis markers: vascular endothelial growth factor (VEGF), von Willebrand factor (vWF), and integrin αvβ3 (αvβ3)
  - Metalloproteinase markers: matrix metalloproteinase 1 (MMP-1; interstitial collagenase); MMP-3 (stromelysin 1); MMP-13 (collagenase 3); and tissue inhibitor of metalloproteinase 1 (TIMP1; collagenase inhibitor) o RT-PCR
  - Tumor necrosis factor-alpha (TNF-α); interleukin-1 (IL-1); IL-2; IL-6; IL-8; IL-10; IL-12 p40 subunit (IL12 p40); IL-17; IL-18; IL-19; IL-20; IL-23 p19 subunit (IL23 p19); interferon-gamma (IFN-γ); interferon-beta (IFN-β); inducible nitric oxide synthase (iNOS); keratin 16 (K16); monocyte chemoattractant protein 1 (MCP1); signal transducer and activator of transcription 1 (STAT1); granulocyte-macrophage colony stimulating factor (GM-CSF); VEGF; and basic fibroblast growth factor (bFGF)

12.1.1.4. Results

The non-compartmental analysis demonstrated similar AUC for the 20 mg twice daily and 40 mg once daily dosing regimens.

The structural PK model was explored using one and two compartment models, and the addition of a time lag in absorption (LAG). However, in comparing models it is not clear whether it was recognized that excluding data from the analysis would result in a decrease in the objective function, which would not necessarily indicate improvement in fit.

The base model provided reasonable estimates of the PK parameters, consistent with prior data (Table 4.3.1.6): mean (%SE) CL/F of 6.98 (7.64) L/h and Vc/F of 82.5 (8.39) L. BSV (%SE) was 42.7 (23.5) % for CL/F and 44.0 (26.9) % for Vc/F.

The final model was a one compartment model and the only covariate that was retained in the model was the effect of MTX use on lag time of apremilast absorption. The final model was validated using a bootstrap approach. The final parameter estimates and the bootstrap estimates are presented. The bootstrap estimates support the final parameter estimates. Co-medication with MTX increased the absorption time-lag by approximately 2 hours.

The PKPD analysis did not attempt to describe an Emax model. The logistic regression analysis indicated that ACR20 was the best outcome variable for further exploration. The parameter best

associated with ACR20 outcome was Cmin. Increasing duration of exposure also increased the probability of ACR20 response. For a typical 81.2 ng/mL increase in Cmin of apremilast (corresponding to the median exposure between the two active treatments) there was an OR (95% CI) for ACR20 response statistically significant odds ratio of response of 1.18 (1.05 to 1.32).

12.1.1.5. Validations

12.1.1.5.1. Validation method

The datasets provided by the Sponsor were imported into Phoenix NLME. Preliminary plots and data analysis were performed using the Phoenix software. Estimation was performed using FOCE-ELS and QRPEM.

The structural model was the same as that chosen by the Sponsor (one compartment model parameterised as V/F and CL/F, with ka and LAG) (Figure 4.3.1.2). However BSV was estimated on all four PK parameters because ETA shrinkage was >0.1 for all four. An omega block was used for V/F and CL/F. An additive residual error model was used.

Covariate modelling was performed using a backward stepwise procedure, with the criteria for removal being p>0.001 and for reinclusion being p<0.0001.

12.1.1.5.2. Validation results

The external validation modelling returned similar estimates for the PK parameters, with the greatest difference being in ka. The external validation covariate modelling also resulted in MTX having an influence on LAG, with a similar magnitude to the submitted results. The plots comparing base and covariate models indicate a good fit of the model to the data. Individual subject predictions also indicate a good fit of the model to the data.

12.1.1.5.3. Comparison of submitted results and validation results

The differences in parameter estimates for ka between the submitted results and the external validation can be explained by:

- Differences in modelling approach, particularly the inclusion of BSV on LAG, and the use of a different residual error model
- Limitations in the data: few samples collected during the absorption phase, even for the intensively sampled data, resulting in difficulty in estimating absorption parameters
- Small sample size

12.1.1.6. Conclusions from study PSA-001

The Sponsor did not make any strong conclusions from this study and did not use the results to inform the Product Information document. The study was used to inform later popPK/PD models.

12.1.1.7. Comments on study PSA-001

The study was not primarily a population PK analysis. The population PK analysis was purely to examine for covariate effects. The analysis was primarily a rich data, two stage approach using WinNonLin, followed by statistical approaches using logistic regression and ROC plot analysis.

The sample size for the population PK model was small. The model was not sufficiently robust to perform simulations, and indeed was not tested with a VPC. Hence the ability of the model to produce useful post-hoc estimates for the entire study population is questionable. Hence, the ability to explore the PKPD relationships was limited, and the Evaluator rejects the findings of the PD analysis.

The primary flaw in the PD analysis is that there was not a sufficient range of doses and plasma concentrations to be able to estimate any PD variables with precision. This limits the utility of the models developed in the analysis for deriving dosing strategies through simulation.

12.1.2. Study PSA-002

12.1.2.1. Objective of the analysis

- To reevaluate the previously reported population PK model (CC-10004-PSA-001-PK) of apremilast using:
  - Sparse data collected in the current phase 3 study at Weeks 4, 16, and 24 (CC-10004-PSA-002) in subjects with PSA
  - Sparse and intensive data collected in the phase 2 study (CC-10004-PSA-001-PK)
  - Pooled relevant data from four phase 1 studies (CC-10004-BA-001, CC-10004-BA-002, CC-10004-PK-008, and CC-10004-PK-010)
- To determine sources of variability in PK parameters of apremilast and identify clinically relevant covariates
- To provide individual secondary exposure parameters of apremilast at steady-state ($C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$) to be used in exposure-response analysis
- To develop exposure-response models based on a pooled analysis of data collected in phase 2 (CC-10004-PSA-001-PK) and phase 3 (CC-10004-PSA-002) studies:
  - To assess the relationship between apremilast exposure and changes in ACR20, ACR50, and HAQDI
  - To explore the relationship between apremilast exposure and occurrence of each of the five most frequent adverse events (AE)

12.1.2.2. Data

The data were obtained from six studies: one Phase 3 and one Phase 2 (conducted in subjects with PSA) and four Phase one (conducted in volunteers) (Table 4.3.2.1). The dose regimens used in the studies were:

- 20 mg twice daily (steady state in subjects with PSA)
- 40 mg once daily (steady state in subjects with PSA)
- 30 mg twice daily (steady state in subjects with PSA)
- 20 mg single dose capsule, fasted and fed (single dose in healthy volunteers)
- 40 mg (as two 20 mg tablets or capsules), fasted and fed (single dose in healthy volunteers)
- 30 mg twice daily for four days (healthy volunteers)
- 50 mg twice daily for four days (healthy volunteers)
- 30 mg twice daily for 6 days in subjects with PSA taking MTX (subjects with PSA)

PK data were available from 258 subjects. Four plasma concentrations were considered to be outliers and were excluded. There were 3130 plasma samples with one to 55 (inclusive) plasma samples per subject (not including samples BLQ). The distribution of the samples is summarised. The age range was 19 to 75 years, weight ranged from 50.4 to 174 kg and CrCL ranged from 36.1 to 315 mL/min (Table 4.3.2.3). There were 174 (67.4%) males, 84 (32.6%) females and 160 (62.0%) subjects with PSA (Table 4.3.2.4).

The exposure response analysis used data from 698 subjects included in Study CC10004-PSA-002 and Study CC-10004-PSA-001-PK. Placebo subjects were included in the analysis. There were 2930 ACR20 observations, 2930 ACR50 observations and 2102 HAQDI observations.

12.1.2.3. Methods

The structural model from Study PSA-001 was accepted and used for further development in Study PSA-002. However, other structural models were also evaluated including a two compartment model. The final structural model was a one-compartment model with Ka and an absorption lag-time, parameterized in terms of apparent clearance (CL/F) and apparent volume of distribution (Vc/F). Between-subject variability of PK parameters was assessed by using a log-normal distribution.

The covariates evaluated were: body weight, CrCL, IBW, LBW, race, disease status (categorised as healthy, PSA and others), sex and smoking status. The formulas used to estimate CRCL were:

$$\mathrm{CRCL_{Male}} = \frac{(140 - \mathrm{Age}) \times \mathrm{weight_{kg}}}{\mathrm{Scr_{mg/dL}} \times 72}$$

$$\mathrm{CRCL_{Female}} = \frac{(140 - \mathrm{Age}) \times \mathrm{weight_{kg}}}{\mathrm{Scr_{mg/dL}} \times 72} \times 0.85$$

The formulas used to estimate IBW were:

$$\mathrm{IBW_{men}} = 50 + 2.3 \times (\mathrm{height_{inches}} - 60)$$
$$\mathrm{IBW_{women}} = 45.5 + 2.3 \times (\mathrm{height_{inches}} - 60)$$

The formulas used to estimate LBW were:

$$\mathrm{LBW_{men}} = \frac{9270 \times \mathrm{weight_{kg}}}{6680 + (216 * \mathrm{BMI_{kg/m^2}})}$$

$$\mathrm{LBW_{women}} = \frac{9270 \times \mathrm{weight_{kg}}}{8780 + (244 * \mathrm{BMI_{kg/m^2}})}$$

A simulation was performed to determine the clinical relevance of the influence of body weight on the PK parameters.

The covariate analyses included age, body weight, IBW, LBW, CRCL, disease status, and sex on CL/F and Vc/F and was performed by using a stepwise forward additive (p-value ≤0.01, δOFV ≤ 6.63 for one df) and backward elimination (p-value >0.001, δOFV >10.83 for one df) approach. Continuous covariates were introduced in the structural model by using a power function. Categorical covariates were introduced in the structural model by using a multiplicative form.

The PD modelling used post-hoc estimates of the secondary PK parameters (Cmax,ss, Cmin,ss, and AUC0-24,ss) as the exposure variables, and ACR20, ACR50 and HAQDI as the PD parameters. Hence in the PD analysis there was one observation per subject.

12.1.2.4. Results

The one compartment model with ka and LAG was selected as the most appropriate model based on stability. There were BSV terms for CL/F, V/F and ka (but not for LAG). The residual error was proportional. Shrinkages to the mean of the random effects of CL/F, Vc/F and Ka estimated with this model were 5.3%, 21.1% and 43.9%, respectively. Although the two compartment model resulted in a lower OFV and also resulted in successful convergence and covariance steps, it was not selected for further development. The typical value (RSE%) were

9.58 (3.18) L/h for CL/F, 104 (3.34) L for Vc/F, 1.57 (13.6) h-1 for ka and 0.272 (17.0) h for lag-time.

The covariate step retained weight, sex, PSA and other/missing disease status as having effects on CL/F and weight, PSA and other/missing disease status as having effects on Vc/F. The bootstrap estimates supported the final model. The VPC indicated a good predictive fit for the model. However, there was little difference in the diagnostic plots between the base model and the final model. The final equation for CL/F was:

$$\mathrm{CL/F} = 11.5 \times (0.638)^{I(\text{disease status} = \text{PSA})} \times (0.761)^{I(\text{disease status} = \text{other or missing})} \times \left(\frac{\mathrm{WT}}{85.7}\right)^{0.309} \times (1.18)^{I(\text{sex=M})}$$

The PK parameters for 467 subjects were predicted using the final PK model. These were then used in the PD analyses. There was an increase in response over time for all the treatment groups, including placebo, that appeared to be dose-dependent for ACR20 and ACR50. Hence placebo response was also included in Emax models for ACR20 and ACR50. There was no clear dose-response relationship for HAQDI.

The model for the effect of AUC0-τ,ss on ACR20 produced precise estimates for placebo effect but not for drug effect. The VPC for the model did not have a good fit to the data indicating this model is not suitable for similations. Although the parameters for the model for ACR50 appeared to be more precise the VPC indicates a poor fit for the model to the data. The model for HAQDI did not produce reliable estimates and the Sponsor did not provide a VPC.

12.1.2.5. Validations

12.1.2.5.1. Validation method

The population PK analysis was performed using Phoenix 64, Build 6.3.0.395, NLME, Pharsight (Centara). Preliminary plots and data analysis were performed using the Phoenix software. Estimation was performed using FOCE-ELS and QRPEM.

The structural model was the same as that chosen by the Sponsor (one compartment model parameterised as V/F and CL/F, with ka and LAG). BSV was estimated on all four PK parameters because ETA shrinkage was >0.1 for all four. An omega block was used for V/F and CL/F. An additive residual error model was used.

Covariate modelling was performed using a backward stepwise procedure, with the criteria for removal being p>0.001 and for reinclusion being p<0.0001. The covariates were added using a power model.

12.1.2.5.2. Validation results

The external validation base model resulted in slightly different estimates for the PK parameters. The estimates for the error parameters were similar for the two approaches. The plots for the base model indicate a good fit of the model to the data. However, the Sponsor's covariate model was not confirmed by the external validation. None of the covariates resulted in a significant reduction in -2LL or AIC.

12.1.2.5.3. Comparison of submitted results and validation results

The external validation covariate modelling employed a backwards stepwise approach, whereas the Sponsor employed a forwards stepwise approach. The process employed by the Sponsor was quite acceptable and followed FDA and EMA guidelines. The popPK model developed by the Sponsor also had good predictive qualities, as evidenced by the VPC. Hence, despite not being able to find a similar model using a different approach, the Evaluator accepts the model developed by the Sponsor.

12.1.2.6. Conclusions on study PSA-002

The Sponsor made the following conclusions from the modelling process

- Typical apremilast $AUC_{0-\tau,ss}$ exposure in subjects with PSA is approximately 1.4 fold of that in healthy subjects
- Lower body weight and being female are associated with higher apremilast exposure. However, the exposure difference attributed to body weight and sex was generally less than 26% and well within the expected between subject variation, and thus deemed not clinically meaningful with regard to dose adjustment by these factors.

12.1.2.7. Comments on study PSA-002

Despite the inability of the external validation to replicate the same covariate model as the Sponsor, the Evaluator considers that the Sponsor has followed appropriate processes in developing their popPK model and that their final model is valid.

Although Study PSA-002 produced an acceptable PK model that was suitable for simulations, the study was not able to produce a suitable PD model. This may be because of the limitations of the data. It is difficult to estimate both EC50 and Emax when the raw data plots clearly indicate that a plateau in effect had not been reached. Hence Emax was inestimable and consequently so was EC50.

Estimation of between subject variability for the PD models was not successful. This is most likely because there was only one observation per subject (post-hoc simulations of secondary PK parameters). Hence the estimation of inter-individual and inter-occasion variability was not viable.

12.1.3. Study PSOR-005

12.1.3.1. Objective of the analysis

- To determine the dose-response relationship of apremilast by using percent reduction of PASI scores in subjects with moderate to severe plaque-type psoriasis
- To characterize the PK of apremilast in subjects with moderate to severe plaque-type psoriasis

The exploratory objective was:

- To explore the relationship between the PK of apremilast and clinical outcomes in subjects with moderate to severe plaque-type psoriasis

12.1.3.2. Data

Data were obtained from a single phase 2B, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, efficacy, and safety study of apremilast in subjects with moderate to severe plaque-type psoriasis. The treatment phase was for 24 weeks. The study also had a 24 week extension phase, during which the placebo subjects were re-randomized to active treatment in a blinded manner. Subjects had a diagnosis of chronic, stable plaque psoriasis at least 6 months prior to screening as defined by: PASI score ≥12 and BSA ≥10%.

The treatment groups were:

- Apremilast 10 mg twice daily, oral administration
- Apremilast 20 mg twice daily, oral administration
- Apremilast 30 mg (one 20 mg tablet and one 10 mg tablet) twice daily, oral administration
- Placebo

Sparse PK sampling was performed on Days 29, 43, 57, 71, 85, 113, 127, 141 and 155 with sampled collected at one of the following four windows: before the morning dose, 0 to3 hours, 3 to 5 hours, or 5 to 8 hours. Intensive PK sampling was performed on Day 99 with samples collected pre-dose and 0.5, 1, 2, 3, 4 and 8 hours after the morning dose. Plasma apremilast was measured using validated chiral liquid chromatography-mass spectrometry methods (LC-MS/MS). The LLOQ was 1.00 ng/mL in plasma.

There were 20 subjects included in the NCA analysis (Table 4.3.3.1). The population PK analysis included 614 plasma samples from 68 subjects (range of 1 to 23 samples per subject). There were 350 subjects included in the PKPD analysis: 89 received 10 mg, 85 received 20 mg, 88 received 30 mg and 88 received placebo. The covariate data for this population are summarised.

12.1.3.3. Methods

The intensive PK data were analysed using NCA and WinNonLin. The PK parameters were: AUC0-8, AUC0-τ, Cmax, Cmin, Tmin, λz, t½, CL/F and V/F.

The population PK analysis was performed using NONMEM Version VI (Level 1.1) using FOCE and INTERACTION. The dataset preparation and raw data analyses were performed using S-PLUS. Bootstrap resampling was used to validate the model using Perl-Speak-NONMEM, and the result of the bootstrap analysis were analysed using R.

The structural model was developed by exploring compartmental analysis. The models were parameterized in clearance terms (CL/F and V/F). The structural model was selected based on the known prior pharmacology of apremilast, a decrease in OFV >6.63 (equivalent to $p < 0.01$) and standard diagnostic plots (fitted and observed concentrations versus time, and CWRES versus time).

Plasma concentrations BLQ were set to 0. There appears to have been no imputation of missing data.

Covariate analysis was performed using visual inspection as well as general additive models in order to identify relevant covariates. The most relevant covariates were formally evaluated with a stepwise forward additive approach by using a p-value of 0.05 and a backward elimination by using a p-value of 0.01. Plots of ETA versus covariate were used to detect trends and to guide the selection of covariate models that were tested (eg, power or linear models). Shrinkage was calculated to determine whether the post hoc PK parameters could be reliably trusted.

The covariates evaluated in the modeling process were: age, sex, BW, LBW, IBW, BMI, race/ethnicity CRCL, and potential interaction with previous MTX treatment.

The PD modeling used a logistic regression analysis to explore relationships between the derived PK parameter estimates and response measures and AE. For PASI-75, logit transformations of the probability of PASI-75 response were evaluated by using linear, second-order polynomial, and Emax PD models. ROC analysis was performed in order to identify the best predictors of response.

12.1.3.4. Results

For the intensive PK data the plots of plasma concentration versus time were consistent with a one-compartment model and therefore suitable for NCA. The PK mean parameter estimates were consistent with previous analyses and were dose proportional in the range 10 mg to 30 mg twice daily at steady state.

For the population PK model the Sponsor decided on a one compartment model with LAG, and with BSV on LAG, ka, V/F and CL/F. The parameter estimates from the base model were consistent with previously known estimates: mean (%SE) CL/F was 8.86 (5.2) L/h, V/F was 94.7 (6.8) L, LAG was 0.351 (17.5) h and ka was 2.52 (39.9) h-1. %BSV (%SE) was 38.3 (18.6) for CL/F and 18.5 (93.9) for V/F. The diagnostic plots are presented.

The only covariate with a significant effect was LBW upon clearance. The final covariate model was:

$$\frac{CL}{F} = 8.72 * \left(\frac{LBW}{58.5}\right)^{0.84}$$

The parameter estimates for the final model are summarised. The final parameter values were supported by the bootstrap estimates.

Diagnostic plots and VPCs were not provided for the final model.

The final model was used to estimate AUC, Cmax and Cmin for the study population for whom outcome data were available. The estimated PK parameters are summarised. For PASI-75, AUC, Cmax and Cmin all had a ROC statistic of 0.81 to 0.82, with Cmin being the best predictor. There were no covariate effects on PASI-75 response. AUC, Cmax and Cmin all had similar predictive capacity for sPGA with a ROC statistic of 0.97. There were no covariate effects on sPGA. DLQI was best predicted by a second order polynomial model. AUC, Cmax and Cmin were all associated with diarrhoea and headache. Nausea and vomiting were best predicted by Cmax.

The ROC analysis indicated the best predictive cut-off point for Cmin in predicting PASI-75 was 155.89 mg/mL: Cmin <155.89 ng/mL gave a 30.0% probability of PASI-75 and ≥ 155.89 ng/mL a 52.4% probability.

12.1.3.5. Validations

12.1.3.5.1. Validation method

The population PK analysis was performed using Phoenix 64, Build 6.3.0.395, NLME, Pharsight (Centara). The dataset used was PSOR-005 Nmdatset. Preliminary plots and data analysis were performed using the Phoenix software. Estimation was performed using FOCE-ELS and QRPEM.

The structural model was the same as that chosen by the Sponsor (one compartment model parameterised as V/F and CL/F, with ka and LAG). BSV was estimated on all four PK parameters because ETA shrinkage was >0.1 for all four. An omega block was used for V/F and CL/F. An additive residual error model was used.

Covariate modelling was performed using a backward stepwise procedure, with the criteria for removal being p>0.001 and for re-inclusion being p<0.0001. The covariates were added using a power model.

12.1.3.5.2. Validation results

The external validation base model resulted in similar estimates for the PK parameters. The diagnostic plots indicated a good fit for the model to the data. The external validation covariate modelling did not confirm an effect of LBW on CL. Although AGE on CL resulted in a significant reduction in -2LL the estimates for SD were not produced by the model, and this model was rejected. Hence, no covariates were accepted as having a significant effect on PK parameters.

The simple covariate search did not indicate a strong relationship between weight and CL.

12.1.3.5.3. Comparison of submitted results and validation results

The external validation did not confirm the results of the Sponsor's model. The discrepancy can be explained by the differences in methodology and the small sample size. The Sponsors model was rejected as not being sufficiently robust.

12.1.3.6. Conclusions on study PSOR-005

The Sponsor concluded that the PK/PD-Safety and ROC analyses suggest that the 30-mg BID treatment may provide the greater probability of PASI-75 response, although it may have a higher probability of manageable AE occurrence compared with the 20-mg BID treatment.

12.1.3.7. Comments on study PSOR-005

In the conclusions of the study report the Sponsor urges caution in interpreting the results of the study because of the small sample size. No definite conclusions were made by the Sponsor and the results do not appear to have informed the Product Information document.

The sample size for the study was small. VPCs were not produced for the final model. The model was not sufficiently robust for predicting the secondary parameters for the study population. Hence, the PD analysis was limited both by the data available and the popPK model.

The Sponsor's final conclusions were also evident from the exploratory plots of the data and the modelling process may not have contributed to the final conclusions.

12.1.4. Study PSOR-008

12.1.4.1. Objective of the analysis

- To re-evaluate the previously reported population PK model (Study PSOR-005, Section 4.3.2) and characterize population PK of apremilast in subjects with moderate to severe plaque psoriasis using data from one Phase 3 study (CC-10004-PSOR-008), one Phase 2 study (CC-10004-PSOR-005-E-LTE) and six Phase 1 studies (CC-10004-BA-001, CC-10004-BA-002, CC-10004-PK-008, CC-10004-PK-010, CC-10004-CP-022, and CC-10004-CP-024)
- To determine sources of variability in PK parameters of apremilast and identify clinically relevant covariates
- To provide individual secondary exposure parameters of apremilast at steady-state: $C_{max,ss}$, $C_{min,ss}$, $AUC_{0-12,ss}$ to be used in exposure-response analysis
- To develop exposure-response models based on a pooled analysis of data collected in Phase 2 (CC-10004-PSOR-005-E-LTE) and Phase 3 (CC-10004-PSOR-008) studies for PASI-50 and PASI-75 scores at Week 16 and sPGA
- To explore the relationship between apremilast exposure and the occurrence of each of the five most frequent AEs, if appropriate data was available

12.1.4.2. Data

The data were obtained from one Phase 3 study (CC-10004-PSOR-008), one Phase 2 study (CC-10004-PSOR-005-E-LTE) and six Phase 1 studies (CC-10004-BA-001, CC-10004-BA-002, CC-10004-PK-008, CC-10004-PK-010, CC-10004-CP-022, and CC-10004-CP-024).

Study (CC-10004-PSOR-008) was a multicentre, randomized, double blind, placebo-controlled, efficacy and safety study of apremilast in subjects with moderate to severe plaque psoriasis. Subjects were treated with apremilast 30 mg twice daily, by oral administration for up to one year. Sparse data were collected at Weeks 24, 32, 36, 40, 44, and 48 (single plasma sample at any time). The outcome measures used in the PKPD analysis were: PASI-50, PASI-75, sPGA and AEs. There were 166 subjects included in the study.

Study PSOR-005 is described in more detail in Section 4.3.3.2. Data from Study CC-10004-BA-001, Study CC-10004-BA-002, Study CC-10004-PK-008, and Study CC-10004-PK-010 were also used in Study PSA-002-PK.

There were a total of 5053 plasma samples from 413 subjects included in the analysis. There were 47 samples excluded, of which 46 from Study PSOR-008 were excluded because dosing times were not available. Demographic characteristics are summarised.

12.1.4.3. Methods

The population PK and PK/PD analyses were performed using NONMEM Version 7.2 with FOCE and the INTERACTION option. Datasets preparation, exploration and visualization were performed using S-PLUS® (Version 8.2, Tibco) or R® (Version 2.15.0), and Microsoft Office®

Excel 2010. Perl-Speak-NONMEM (PsN Version 3.5.3) was used to evaluate/validate the model and the results were analyzed by R® (Version 2.15.0). Generalized linear/nonlinear mixed-effects models for efficacy and safety endpoints were performed using NONMEM (Version 7.2) and/or R® (Version 2.15.0 or greater).

The structural model was taken from the previous study, Study PSOR-005, and was a one compartment model, parameterised as CL/F and V/F, with ka and LAG. BSV was evaluated on each of the PK parameters, and residual variability was evaluated with additive, proportional or combined additive and proportional models.

The model selection criteria were:

- Standard statistical criteria of goodness-of-fit such as the log-likelihood difference between rival models (i.e. a decrease in MOF value, accuracy of parameter estimation).
- Diagnostic plots: DV versus PRED and IPRED; CWRES versus PRED, CWRES versus time, QQ plot of CWRES.
- AIC, OFV, fitted and observed concentrations versus time

The covariates were: age, sex, race/ethnicity, WT, serum creatinine, drug-drug interaction with concomitant drugs (MTX; or CYP3A, CYP1A2 and CYP2A6 substrates), and smoking status. CRCL, LBW and IBW were estimated using the same methods as described in Section 4.3.2.3. The covariate modelling was performed by using a stepwise forward additive (p-value ≤0.01 or δOFV ≤6.63 for one df) and backward elimination (p-value >0.001 or δOFV >10.83 for one df) approach. Continuous covariates were introduced in the structural model by using a power function. Categorical covariates were introduced in the structural model by using a multiplicative form.

The PKPD models used an indirect response Emax model to relate apremilast exposure to PASI-75, PASI-50 and sPGA. Logistic regression models were used to relate apremilast exposure (PK parameters and duration of exposure) to AEs.

The performance of the final population PK model of apremilast was evaluated with nonparametric bootstrap resampling and VPC.

Samples BLQ were not included in the analysis. Missing data were not imputed.

12.1.4.4. Results

The base model consisted of a one-compartment model with lag time of absorption, mixed residual error model, a block omega on CL/F and Vc/F and a separate omega on Ka. The parameter estimates from the base model were consistent with the estimates from previous models. The diagnostic plots indicated an appropriate specification of the error model.

The final model retained effects of sex and disease status on CL/F, and WT on Vc/F. The diagnostic plots for the final model also indicated an appropriate specification of the model. The final equation for CL was:

$$\mathrm{CL/F} = 9.25 \times (0.801)^{I(\text{disease status = PSOR})} \times (1.09)^{I(\text{disease status = other or missing})} \times (1.31)^{I(\text{sex=M})}$$

where $I(\cdot)$ denotes an indicator function.

Hence the model indicates CL/F is decreased by around 20% in subjects with moderate to severe plaque psoriasis (compared to healthy subjects) and by approximately 30% in female (compared to male subjects). The geometric mean (geometric CV%) posthoc estimates were 117 (28.0) L for V/F, 9.84 (47.2) L/h for CL/F, 1.8 (63.4) h-1 for ka and 8.28 (28.3) h for t½, 301 (47.0) ng/mL for Cmax,ss and 95 (108) ng/mL for Cmin,ss. The VPC indicated an acceptable predictive performance for the model.

The plots of response over time, by dose level, indicate increasing response over time and with increasing dose for all three efficacy outcome measures: PASI-75, PASI-50 and sPGA. However, there was no plateau of effect with increasing dose, indicating the Emax had not been achieved. Emax models were still fitted to the data. For the Emax model for PASI-75, E50 in terms of AUC was 1750 ng•h/mL but estimates for BSV were not provided (Table 4.3.4.8). For the Emax model for PASI-50, E50 in terms of AUC was 758 ng•h/mL but estimates for BSV were not provided. For the Emax model for sPGA, E50 in terms of AUC was 1290 ng•h/mL but estimates for BSV were not provided. The Sponsor concluded that the 30 mg twice daily regimen offered the highest probability of response for each of the three outcome measures.

Formal analysis of exposure response with regard to AEs was not performed due to the low frequency of the AEs in the study population.

12.1.4.5. Validations

12.1.4.5.1. Validation method

The population PK analysis was performed using Phoenix 64, Build 6.3.0.395, NLME, Pharsight (Centara). The dataset used was the pkdat datset. Preliminary plots and data analysis were performed using the Phoenix software. Estimation was performed using FOCE-ELS and QRPEM.

The structural model was the same as that chosen by the Sponsor (one compartment model parameterised as V/F and CL/F, with ka and LAG). BSV was estimated on all four PK parameters because ETA shrinkage was >0.1 for all four. An omega block was used for V/F and CL/F. An additive residual error model was used.

Covariate modelling was performed using a backward stepwise procedure, with the criteria for removal being $p>0.001$ and for re-inclusion being $p<0.0001$. The covariates were included using power models.

12.1.4.5.2. Validation results

The parameter estimates from the external validation base model were consistent with those from the Sponsor's base model. The omega estimates are presented. The diagnostic plots indicate a good fit for the model to the data.

The covariate search retained the effects of disease state on CL/F and MTX on LAG. There was no covariate effect on V/F. However, the estimate for the effect of disease state on CL/F was implausibly high ($e^{-4.14}$ which represents a 98% reduction on CL/F). LAG was increased by approximately 50% by comedication with MTX. However, in the opinion of the Evaluator, the model requires further work.

12.1.4.5.3. Comparison of submitted results and validation results

The external validation model confirmed an effect of disease state on CL/F but did not confirm the effect of weight on V or SEX on CL/F. This might be explained by the more stringent hypothesis tests used for inclusion in the covariate model as performed in the external evaluation.

12.1.4.6. Conclusions on study PSOR-008

The main conclusions of the Sponsor from the study were:

- CL/F in subjects with moderate to severe plaque psoriasis was approximately 20% slower (9.25 L/h versus 7.4 L/h) than that in healthy subjects. CL/F in female subjects with moderate to severe plaque psoriasis were approximately 31% slower (7.4 L/h versus 9.7 L/h) than that in male psoriasis subjects. However, the exposure differences attributed to sex and disease status were approximately 31% and approximately 20%, respectively, which were within the expected BSV for CL/F. The results suggest that no dose adjustment by sex is deemed necessary in patients with moderate to severe plaque psoriasis.

- Exposure-response analyses suggest that the 30 mg twice daily treatment is likely to provide greater probability of achieving PASI-75, PASI-50 and sPGA responses compared to the 20 mg twice daily or 10 mg twice daily treatments.

12.1.4.7. Comments on study PSOR-008

The Evaluator accepts that subjects with moderate to severe plaque psoriasis will have reduced clearance compared to healthy subjects. However, the evaluator rejects that gender will have an effect on PK parameters to a greater extent than body size (weight). The external validation did not confirm an effect of gender on clearance. In addition, the covariate for gender may represent a weight grouping rather than an effect of gender, as such. The known pharmacology of apremilast does not provide a plausible explanation as to why gender should have an observable effect on CL/F, other than the difference in body size between the genders.

The Evaluator rejects the PD analysis for the reason that the Sponsor did not demonstrate that a maximum effect had been achieved, and consequently the model could not estimate Emax, and therefore EC50. A linear model would have been more appropriate for the PD data. The Sponsor's final conclusions with regard exposure-response could have been made from the exploratory data plots and did not benefit from the PKPD modelling process.

12.1.5. Study RA-002

12.1.5.1. Objective of the analysis

- To characterize the pharmacokinetics (PK) of apremilast in subjects with RA using NCA methods.
- To perform population PK modeling of apremilast using:
  - Intensive and sparse data collected in the current phase 2 study at Weeks 4, 12, 16, and 24 (Study CC-10004-RA-002) in patients with RA;
  - Pooled relevant data from four Phase 1 studies (CC-10004-BA-001, CC-10004-BA-002, CC-10004-PK-008, and CC-10004-PK-010)
- To determine sources of variability in PK parameters of apremilast and identify clinically relevant covariates
- To provide individual secondary exposure parameters of apremilast at steady-state ($C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-\tau,ss}$) that may be used in exposure-response analysis.

12.1.5.2. Data

Data were extracted from study CC-10004-RA-002 and four Phase 1 studies.

Study CC-10004-RA-002 was a randomised, double blind, placebo controlled, efficacy and safety study of two dose regimens of apremilast in subjects with RA who had an inadequate response to MTX. All subjects received concomitant MTX during the study. The dose regimens were:

- Apremilast 20 mg, oral administration twice daily
- Apremilast 30 mg, oral administration twice daily

There was a 7 day dose tritation period at commencement of treatment. Intensive PK sampling was performed on 32 subjects at Visit 4 (Week 12) (pre dose and 0.5, 1, 2, 3, 4, and 8 hours after the morning dose) and sparse data were collected at Visits 3, 5 and 6 (pre dose and at either 0 to 3, 3 to 5 or 5 to 8 hours post dose).

The NCA used only data from Study CC-10004-RA-002 and used the intensive samples for the 32 subjects: 18 subjects from the 20 mg twice daily group, and 14 from the 30 mg twice daily.

The population analysis included 2779 samples (of which 2767 had measurable concentrations) from 158 subjects. The demographic characteristics are summarised. There were 106 (67.1%) males, 52 (32.9%) females and the age range was 19 to 81 years.

12.1.5.3. Methods

The NCA was performed using WinNonLin. The population PK analysis was performed using NONMEM.

Model evaluation and selection of the structural model was based on:

- Standard statistical criteria of goodness-of-fit such as the log-likelihood difference between rival models (i.e., a decrease in MOF and accuracy of parameter estimation).
- Diagnostic plots: DV versus PRED and IPRED; CWRES versus PRED, CWRES versus time and time after last dose; and QQ plot.

Concentration values that were reported as BLQ were set to zero for PK and statistical analyses.

The covariate modelling employed a stepwise forward additive (p-value ≤ 0.01, δOFV ≤ 6.63 for one df) and backward elimination (p-value > 0.001, δOFV > 10.83 for one df) approach. Continuous covariates were introduced in the structural model by using a power function. Categorical covariates were introduced in the structural model by using a multiplicative form. The covariates explored in the model were: body weight, CRCL, IBW, LBW, age, creatinine clearance, race, disease status, gender and smoking status. CRCL, LBW and IBW were estimated using the same methods as described.

12.1.5.4. Results

The plots of the intensive sampled plasma concentrations versus time were consistent with a one-compartment model. For the NCA, the Sponsor reported dose proportionality for the 20 mg and 30 mg dose levels, but there were some significant differences between the parameters for the two dose levels, most strikingly for V/F and CLss/F. However, this study was not a crossover design and the differences between these parameter estimates may be due to demographic characteristics of the subjects rather than a dose effect.

For the population PK model, the structural model was re-evaluated with one and two compartment models, with and without LAG. The most appropriate model was again the one-compartment model with Ka and LAG, parameterised with CL/F and V/F. The interindividual error model was a block omega on CL/F and Vc/F and a separate omega on Ka. The residual error model was proportional.

The parameter estimates from the structural model were consistent with the previous models discussed in this report and were precise. The diagnostic plots indicated an appropriate specification of the model.

The covariate modelling also used arguments of clinical relevance in the modelling rationale. Although the effect of LBW on CL/F had higher statistical significance than that of body weight, body weight was used in the final model for the following reasons:

- Body weight was deemed to be more clinically relevant than LBW
- LBW is derived from body weight, gender and BMI, so a model including the effects of body weight and gender on CL/F was considered as an alternative to the effect of LBW on CL/F

The final model retained the effects of body weight, gender and disease status on CL/F, and the effect of body weight on Vc/F. The diagnostic plots indicated an appropriate specification of the model. The final equation for CL/F was:

$$\mathrm{CL/F} = 11.2 \times (0.679)^{I(\text{disease status = RA})} \times (1.01)^{I(\text{disease status = other or missing})} \times \left(\frac{\mathrm{WT}}{79.9}\right)^{0.692} \times (1.15)^{I(\text{sex=M})}$$

The final parameter estimates are presented. The bootstrap estimates were in agreement with the final model parameter estimates. The VPC demonstrated an acceptable fit for the model to the data.

The posthoc parameter estimates are summarised. Studies in subjects with RA had similar V, lower CL/F and longer t½ compared with those conducted in healthy subjects. The secondary parameters are summarised. For equivalent dosing, studies in subjects with RA had up to two-fold higher overall exposure, as measured by AUC and Cmax than studies in healthy subject.

12.1.5.5. Validations

12.1.5.5.1. Validation method

The population PK analysis was performed using Phoenix 64, Build 6.3.0.395, NLME, Pharsight (Centara). The dataset used was the pkdata datset. Preliminary plots and data analysis were performed using the Phoenix software. Estimation was performed using FOCE-ELS and QRPEM.

The structural model was the same as that chosen by the Sponsor (one compartment model parameterised as V/F and CL/F, with ka and LAG). BSV was estimated on all four PK parameters because ETA shrinkage was >0.1 for all four. An omega block was used for V/F and CL/F. A power residual error model was used.

Covariate modelling was performed using a forward stepwise procedure, with the criteria for inclusion being $p<0.001$ and for elimination being $p>0.0001$. Continuous covariates were introduced in the structural model by using a power function. Categorical covariates were introduced in the structural model by using a multiplicative form.

12.1.5.5.2. Validation results

The parameter and error estimates from the external validation structural model were consistent with the Sponsor's model. The plots of ln plasma concentration versus TAD (by study) indicate that a one compartment model would describe the data. There were some differences attributable to the different error models. The diagnostic plots for the external evaluation model indicated a good fit for the model to the data.

The covariate model retained the effect of WT on V/F, and WT, disease status and SEX on CL/F. Although there were differences in the magnitude of the parameter estimates, the effects of weight and disease status on CL/F were similar for the external validation model.

12.1.5.5.3. Comparison of submitted results and validation results

Although there were differences in parameter estimates the external validation model was in agreement with the Sponsor's model. The differences were primarily in the absorption parameters and in V/F, and the estimation of these parameters was limited by the paucity of data during the absorption phase.

12.1.5.6. Conclusions on study RA-002

The Sponsors conclusions from Study RA-002 were:

- Typical apremilast $AUC_{0-\tau,ss}$ exposure in patients with RA is approximately 47% higher than that of healthy subjects.
- Lower body weight and being female are associated with higher apremilast exposure. However, the exposure difference attributed to body weight and gender was generally less than 25% and well within the expected between subject variation, and thus deemed not clinically meaningful with regard to dose adjustment by these factors.

12.1.5.7. Comments on study RA-002

The PK model developed in Study RA-002 had good predictive properties, as evidenced by the VPC. The external validation also confirmed the Sponsor's model. The Sponsor did not attempt a PD analysis

12.2. Evaluator's conclusions on population pharmacokinetics

The modelling processes were conducted and reported in accordance with published guidelines.[7] However, in the opinion of the evaluator, within this guideline there is considerable latitude in methodology and in interpretation of results.

The base structural model was similar for all five studies and was confirmed by the external validations. The error model used by the sponsor differed from the external validations in that the sponsor did not estimate Between Subject Variability (BSV) for Lag time of absorption (LAG). The evaluator considers a BSV for LAG to be appropriate because of all the parameters it appeared to be the one with the greatest variability.

Goodness-of-fit plots were provided for all of the models and indicated an appropriate specification for the models. However, Visual Predictive Checks (VPCs) were not provided for all of the models. The best model, as judged by VPC, of all the studies was RA-002.

The covariate models were developed using all the available covariate data. The covariate model building process used by the sponsor was less rigorous than that believed to be appropriate by the evaluator. The p-values used in the covariate modelling by the sponsor were overly generous given the large quantity of data available.

It is not clear how sex would influence the apparent clearance (CL/F) of apremilast, which questions the plausibility of the models. This concept does not appear to be supported by the known disposition of apremilast. Apremilast has multiple pathways of elimination and it is not clear whether sex would influence any of these pathways. Hence, in the opinion of the evaluator, sex may be a confounder for the effect of body weight. The known pharmacology of apremilast does not provide a plausible explanation as to why gender should have an observable effect on CL/F, other than the difference in body size between the genders.

No dosing regimens were simulated from the models. In the opinion of the evaluator, the models would not be appropriate for simulating dosing strategies in other populations (for example, paediatric).

The modelling process does not appear to have influenced the proposed dosing regimen for apremilast. This dosing regimen appears to be based upon the Phase II and Phase III studies rather than upon modelling and simulation. Hence, although the pharmacodynamic models were (in the opinion of the evaluator) flawed, they did not influence the dosing strategy.

The results of the population PK/PD models do not appear to have informed the sections of the PI document relating to pharmacokinetics or pharmacodynamics. The models do indicate that CL/F is significantly reduced in disease states and this information should be included. However, as the dosing strategy is based on the actual clinical trial data, there is no need to advise dosing adjustment because of disease state. There were no other findings from the studies that might be used to inform the PI document (for example, use in special populations).

[7] European Medicines Agency, "Guideline on Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06)", 21 June 2007.

13. First round benefit-risk assessment

13.1. First round assessment of benefits

The population PK/PD modelling suggested a concentration-response relationship exists for apremilast for all the three indications studied: active psoriatic arthritis in adult patients, adult patients with moderate to severe plaque psoriasis, and adult patients with RA who had an inadequate response to MTX. The studies did not successfully identify the nature of these concentration response relationships because of limitations in the data and in the modelling approach. Overall, the studies did not indicate that dosing modification was required on the basis of physical or demographic characteristics.

The pharmacokinetics of apremilast is affected by disease state for each of the three study populations (active psoriatic arthritis in adult patients; adult patients with moderate to severe plaque psoriasis, and adult patients with RA who had an inadequate response to MTX). Clearance is decreased compared to healthy volunteers for all three populations. However, the dosing regimens for each indication have been based on clinical trial data and do not require modification on the basis of the pharmacokinetic studies. The sponsor did not simulate any alternative dosing strategies from the population PK/PD models.

The Summary of Clinical Pharmacology states that clearance is reduced by 30% in females compared to males. However, the population pharmacokinetic studies are not sufficiently robust to justify this statement. The known pharmacology of apremilast does not provide a plausible explanation as to why gender should have an observable effect on CL/F, other than the difference in body size between the genders. The statement regarding clearance and gender has not been included in the PI document.

13.2. First round assessment of risks

The population PK/PD studies did not indicate a concentration-response relationship between apremilast and adverse effects. However, the analyses were limited by the paucity of AE data and there were insufficient data to be able to identify such relationships.

13.3. First round assessment of benefit-risk balance

The results of the population PK/PD studies do not appear to alter the benefit-risk balance.

14. First round recommendation regarding authorisation

The evaluator does not have any objections arising from the population PK/PD studies to the approval of apremilast for the indications of active psoriatic arthritis in adult patients, adult patients with moderate to severe plaque psoriasis, and adult patients with RA who had an inadequate response to MTX.

15. Clinical questions

· What are the proposed mechanisms by which sex would influence the CL/F of apremilast?

15.1. Pharmaceutical sub-committee, section 31 questions

· Please justify the choice of a one compartment pharmacokinetic model given that a 2 compartment pharmacokinetic model was found in some of the studies (for example, PSA-

001 and PSA-002) to be the model which provided the best fit to the concentration-time data.

- Please justify the choices made in the covariate model building process. The Pharmaceutical Sub-Committee noted that the decrease in clearance (CL) between patients with disease and healthy subjects may reflect a difference in age. Provide an analysis of the effects of each of the covariates: sex, body weight (lean and total), age, and disease state on the PK of apremilast to distinguish these.
- The Pharmaceutical Sub-Committee noted that modelling showed a decrease in clearance in females compared with males, and a decrease in clearance in patients when compared with healthy volunteers. Noting that the patient population was on average older and heavier than the healthy population, your company is asked to clarify whether the decrease in CL between males and females reflects a difference in lean body weight.
- Given the apparent finding that CL is approximately 30% lower in females than in males, the PSC is of the view that if this relationship is confirmed then a dose reduction may be recommended for females. Your company is requested to address this issue including performing simulations from the model in regards to their impact on dose recommendations.
- Please amend the proposed Australian PI to state the pharmacokinetic parameters (including CL values) in patients and to include relevant findings of covariate re-analysis. The following information should be included in the PI and, where relevant, in the Consumer Medicines Information (CMI).
  - PSA-002 found a different CL for patients with PsA
  - PSOR-005 only found Lean Body Weight (LBW) to be a factor, not disease
  - PSOR-008 found CL was reduced 20% in patients with psoriasis
  - RA-002-PK found reduced CL by 30% (not 11.2L/h, but 7.6 L/h) for patients with RA, an effect of weight and gender on CL, and of weight on volume of distribution (V).
- As part of its response concerning dose, the sponsor should provide analyses using clinical trial data that explore the apparent differences in efficacy and safety of the doses investigated (20 mg and 30 mg) and the benefit-risk profile at each dose level.

16. Second round evaluation of clinical data

- *Please justify the choice of a one compartment pharmacokinetic model given that a 2 compartment pharmacokinetic model was found in some of the studies (for example, PSA-001 and PSA-002) to be the model which provided the best fit to the concentration-time data.*

Sponsor's response

The key statement from the Sponsor in response to this question is: "The 1-compartment models based on Phase 2 and Phase 3 studies are also consistent with the plasma concentration versus time profile observed in Phase 1 studies using the intensive PK sampling approach, in which the plasma apremilast concentration after achieving the maximum observed plasma concentration (Cmax) declines in a monophasic/monoexponential manner (e.g., CC-10004-CP-022 and CC-10004-CP-024). Therefore, the 1-compartment PK model was the model that appropriately reflected the PK of apremilast, and thus was chosen for the population PK analysis."

The Sponsor further responded that overall a one compartment model performed better than a two compartment. By individual study:

- In Study CC-10004-PSA-001-PK the one compartment model minimised successfully and had the lowest OFV.
- In Study CC-10004-PSA-002-PK a two compartment model had a lower OFV than the one compartment but the Sponsor states "The 2-compartment model was tested but did not perform well and did not significantly improve the quality of fit". This conclusion is on the basis of the diagnostic plots (Figure 13.1.1 and Figure 13.1.2).
- In Study CC-10004-PSOR-005-PK a one compartment model minimised successfully and had the lowest OFV.
- In Study CC-10004-PSOR-008-PK, although a two compartment model had a lower OFV than the one compartment, the Sponsor states, in reference to the one compartment model: "This base model was stable and resulted in a successful covariance step". The two compartment model did not produce a covariance step.
- In Study CC-10004-RA-002-PK the one compartment model minimized successfully and resulted in a covariance step. The two compartment model did not minimize successfully.

Evaluator's comments

The Sponsor's response is acceptable. The Sponsor has provided sufficient justification for using the one compartment model in each of the studies.

- *Please justify the choices made in the covariate model building process. The Pharmaceutical Sub-Committee noted that the decrease in clearance (CL) between patients with disease and healthy subjects may reflect a difference in age. Provide an analysis of the effects of each of the covariates: sex, body weight (lean and total), age, and disease state on the PK of apremilast to distinguish these.*

Sponsor's response

The Sponsor has provided a detailed description of the covariate model building process for Study CC-10004-PSA-008-PK. The Sponsor applied a forward-backwards stepwise approach to the covariate model building, using a p-value ≤0.01 or ΔOFV ≤6.63 for forwards inclusion and a p-value ≤0.001 or ΔOFV ≤10.83 for backwards elimination. This model building process resulted in a covariate model that included the effects of sex and disease status on CL/F and total body weight on Vc/F. Age and body weight on CL/F did not contribute significantly to the model and were excluded. The Sponsor concluded that "the effects of disease status and sex are more important than age and body weight on CL/F".

However, the Sponsor also comments: "Sex and body weight are two confounding demographical factors and are inseparable since body weight in female subjects is generally lower than in male subjects. In a study population predominantly with male subjects, body weight is a statistically significant factor on CL/F (CC-10004-PSA-002-PK). If male and female subjects are well balanced in a study population (CC-10004-PSOR-008-PK), the effect of body weight is overshadowed by the effect of sex as a category factor".

Evaluator's comments

The Sponsor's response is acceptable. The Sponsor has applied methodology that is consistent with the Guideline on Reporting the Results of population Pharmacokinetic Analyses CHMP/EWP/185990/06. The results of the study are internally valid (i.e. consistent with the data, and the analysis). The Sponsor appears to acknowledge that the effects of sex and body weight may confound the other. In the opinion of the Evaluator, in the absence of a physiological

explanation for the effect of sex on clearance, caution should be exercised in applying this information to the general patient population.

- *The Pharmaceutical Sub-Committee noted that modelling showed a decrease in clearance in females compared with males, and a decrease in clearance in patients when compared with healthy volunteers. Noting that the patient population was on average older and heavier than the healthy population, your company is asked to clarify whether the decrease in CL between males and females reflects a difference in lean body weight.*

Sponsor's response

The key statements from the Sponsors response are: "The sponsor also agrees that the decrease in CL/F between males and females may partially reflect a difference in lean body weight. However, the results of the population PK analysis demonstrated the effect of disease and sex were much more significant than the effects of LBW and weight".

The Sponsor argues that the results of the covariate modelling for Study CC-10004-PSOR-008-PK demonstrated in the first step of the covariate modelling greater reductions in OFV with effects on CL/F of weight and sex than with LBW. In subsequent steps weight was also excluded. The Sponsor also argues that LBW is a composite of sex, weight and BMI, implying that LBW should not be included in the same model as sex, weight or BMI.

Evaluator's comments

The Sponsor's response is acceptable. The Sponsor has evaluated LBW in the covariate modelling process for Study CC-10004-PSOR-008-PK. In common with Question 2, the Sponsor has applied methodology that is consistent with the Guideline on Reporting the Results of population Pharmacokinetic Analyses CHMP/EWP/185990/06. The results of the study are internally valid (i.e. consistent with the data, and the analysis).

- *Given the apparent finding that CL is approximately 30% lower in females than in males, the PSC is of the view that if this relationship is confirmed then a dose reduction may be recommended for females. Your company is requested to address this issue including performing simulations from the model in regards to their impact on dose recommendations.*

Sponsor's response

The Sponsor has performed simulations using the final covariate model from Study CC-10004-PSOR-008-PK for a population of 1000 "male and female subjects with moderate to severe plaque psoriasis with the same characteristics as the observed subject population". The Sponsor argues that there is considerable overlap of the simulated plasma concentration versus time distributions between the male and female populations. The Sponsor also argues there is a considerable overlap of the distributions for males and females for Cmax and AUC. On the basis of the similarity between these distributions, the Sponsor argues that dose adjustment for females is not necessary.

Evaluator's comments

The Sponsor's response is acceptable. The simulations were performed using appropriate populations and an appropriate model. In the opinion of the Evaluator the distributions of plasma concentration versus time, of Cmax and of AUC are sufficiently similar for males and females to make dose adjustment on the basis of sex unnecessary.

- *Please amend the proposed Australian PI to state the pharmacokinetic parameters (including CL values) in patients and to include relevant findings of covariate re-analysis. The following*

information should be included in the PI and, where relevant, in the Consumer Medicines Information (CMI).

- *PSA-002 found a different CL for patients with PsA*
- *PSOR-005 only found Lean Body Weight (LBW) to be a factor, not disease*
- *PSOR-008 found CL was reduced 20% in patients with psoriasis*
- *RA-002-PK found reduced CL by 30% (not 11.2L/h, but 7.6 L/h) for patients with RA, an effect of weight and gender on CL, and of weight on volume of distribution (V).*

Sponsor's response

The Sponsor has declined to make any of the requested changes to either the PI or the CMI. The reasons for declining can be paraphrased as:

- Some of the differences in results for CL between studies can be explained by differences in the demographics of the study subjects. The Sponsor states: "After taking the effects of covariates into account …. , apremilast CL/F values for subjects with psoriatic arthritis, rheumatoid arthritis, and psoriasis were determined to be 7.34 L/h, 7.6 L/h, and 7.4 L/h, respectively".
- Study CC-10004-PSOR-005-PK was undertaken at an early stage of development and used data from only one study.
- The strategy of dosing is based on clinical trial data and not on the PK analysis
- The covariate analyses were intended to provide understanding of the sources of variation in a given study population and were not intended to provide instructions for patients and clinicians.

Evaluator's comments

In the opinion of the Evaluator this response is not acceptable. The PI document is the primary source of drug information about a chemical entity, especially when a new chemical entity is first authorised. Hence, important sources of variation in PK and PD (such as disease state) should be stated in the PI. The Evaluator agrees with the Sponsor that the information from Study CC-10004-PSOR-005-PK should not be included in the PI because the Evaluator does not consider the study to be sufficiently robust to make any definite conclusions. In the case of the CMI, the Evaluator does not consider this information needs to be included because it is unlikely to influence any choices a consumer may make, or provide instruction on the safe and effective use of the medicine.

- *As part of its response concerning dose, the sponsor should provide analyses using clinical trial data that explore the apparent differences in efficacy and safety of the doses investigated (20 mg and 30 mg) and the benefit-risk profile at each dose level.*

Sponsor's response

The Sponsor argues that in subjects with active psoriatic arthritis the Phase 3 clinical trial data as well as the PKPD analysis from Study CC-10004-PSA-002-002-PK demonstrated greater efficacy for the 30 mg dose level over the 20 mg dose level. The clinical trial data are summarised in Table 13.1.1. There were also greater improvements in quality of life and functional endpoints with the 30 mg dose compared to the 20 mg. The PKPD analysis also indicated a higher probability of achieving ACR20 response with the 30 mg dose level.

The Sponsor has provided summary tabulations of adverse events. Overall, there were similar rates of AEs in the 20 mg and 30 mg treatment groups. However, there were higher rates of diarrhoea, nausea and headache.

The Sponsor argues that taking into account the greater efficacy of the 30 mg dose form, and similar safety profile, the risk benefit profile of the 30 mg dose is better than that of the 20 mg.

Evaluator's comments

The Sponsor's response is acceptable. The PKPD data also support a clear dose response relationship for apremilast efficacy, with greater response at the 30 mg dose level, but no clear dose response relationship for adverse effects. Hence the PKPD data also support the 30 mg dose level over the 20 mg.

17. Second round benefit-risk assessment

17.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of apremilast in the proposed usage are unchanged from those identified in the first round.

17.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of apremilast in the proposed usage are unchanged from those identified in the first round.

17.3. Second round assessment of benefit-risk balance

The benefit-risk balance is unchanged from that identified in the first round.

18. Second round recommendation regarding authorisation

The evaluator does not have any objections arising from the population PK/PD studies to the approval of apremilast for the indications of active PsA in adult patients, adult patients with moderate to severe plaque psoriasis, and adult patients with RA who had an inadequate response to MTX.

19. References

- Caitlin CS, Feldman SR, Krueger JG, et al. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol 2004; 50: 859-866.
- Kwok T and Pope JE. Minimally important difference for patient reported outcomes in psoriatic arthritis: Health Assessment Questionnaire and pain, fatigue and global analogue scales. J Rheumatol 2010; 37: 1024-1028.
- Mease PJ. Psoriatic Arthritis: update on pathophysiology, assessment and management. Ann Rheum Dis 2011; 70: i77-i84.

- Mease PJ, Woolley JM, Bitman B, et al. Minimally important difference in Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient ability to patient-rated importance and satisfaction. J Rheumatol 2011a; 38: 2461-2465.
- Schafer PH, Parton A, Gandhi AK, et al. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. Br J Pharmacol 2010; 159: 842-855.
- Schett G, Elewaut D, McInnes IB, et al. How Cytokine Networks Fuel Inflammation: Toward a cytokine-based disease taxonomy. Nat Med 2013; 19: 822-824.

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