Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Abatacept

Proprietary Product Name: Orencia

Sponsor: Bristol-Myers Squibb Australia Pty Ltd.

February 2019

TGA Health Safety Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR20	ACR criteria for 20% improvement
ACR50	ACR criteria for 50% improvement
ACR70	ACR criteria for 70% improvement
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALB	Albumin
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANCOVA	Analysis of covariance
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{ss}	Area under the serum concentration-time curve at steady-state
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	Body mass index
BMS	Bristol-Myers Squibb
BSA	Body surface area
BUN	Blood urea nitrogen
BWT	Baseline body weight
CASPAR	Classification criteria for psoriatic arthritis
C_{avg}	Average concentration
$C_{av,ss}$	Time-averaged serum concentration at steady-state
CGFR	Baseline calculated glomerular filtration rate

Abbreviation	Meaning
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed concentration
$C_{max,ss}$	Peak serum concentration at steady-state
CMH	Cochran-Mantel-Haenszel
C_{min}	Trough serum concentration
$C_{min,ss}$	Trough serum concentration at steady-state
COPD	Chronic obstructive pulmonary disease
CPDAI	Composite Psoriatic Disease Activity Index
CRP	C-reactive protein
CSR	Clinical study report
CTLA	Cytotoxic T-lymphocyte-associated protein
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
DAS28	Disease Activity Score 28
DAS28-CRP	Disease Activity Score 28 C-Reactive Protein
DLQI	Dermatology Life Quality Index
DMARD(s)	Disease modifying anti-rheumatic drug(s)
ECL	Electrochemiluminescence assay
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
E_{max}	Maximal effect/ efficacy
E-R	Exposure-response
EU	European Union
F	Bioavailability
FACIT	Functional Assessment of Chronic Illness Therapy

Abbreviation	Meaning
FDA	Food and Drug Administration
FORM	Subcutaneous formulation
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HAQ	Health Assessment Questionnaire
HAQDI	Health Assessment Questionnaire Disability Index
IA	Intra-articular
ICH	International Conference of Harmonisation
Ig	Immunoglobulin
IGA	Investigator Global Assessment
IM	Intramuscular
IR	Incidence rate
ITT	Intent-to-treat
IV	Intravenous
JIA	Juvenile idiopathic arthritis
JSN	Joint space narrowing
k_a	Absorption rate constant
LDAS	Low Disease Activity Score
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
LOCF	Last observation carried forward
LT	Long term
MA	Marked anomaly
MCID	Minimally clinically important difference
mCPDAI	Modified Composite Psoriatic Disease Activity Index
MCS	Mental component summary (of SF-36 questionnaire)

Abbreviation	Meaning
MDA	Minimal disease activity
MRI	Magnetic resonance imaging
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NAb	Neutralising antibodies
NSAIDS	Non-steroidal anti-inflammatory drugs
OL	Open label
PAC	Patient alert card
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PASI50	PASI 50% improvement
PCS	Physical component summary (of SF-36 questionnaire)
pcVPC	Prediction-corrected visual predictive check
PD	Pharmacodynamics
PK	Pharmacokinetics
popPK	Population pharmacokinetic
PPK	Population pharmacokinetics
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
p-y	Patient-years
Q	Inter-compartmental clearance
QC	Quality control
QOL	Quality of life
RA	Rheumatoid arthritis
ROC	Receiver operating characteristic
SA	Scientific Advice

Abbreviation	Meaning
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCS	Summary of Clinical Safety
SD	Standard deviation
SDC	Smallest detectable change
SE	Standard error
SF-36	Short Form 36 questionnaire
SHS	Sharp/van der Heijde Score
SJC	Swollen joint count
SmPC	Summary of product characteristics
ST	Short term (double blind short term period)
STER	Corticosteroid
SWOL	Baseline swollen joint count
T50	Time to 50% of E_{max}
TB	Tuberculosis
TL	Target lesion
TL50	TL 50% improvement
TNF	Tumor necrosis factor
TNFi-	Tumor necrosis factor inhibitor-
US	United States of America
VAS	Visual Analog Scale
VC	Central volume
VP	Peripheral volume

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	10 January 2018
Date of entry onto ARTG:	12 January 2018
ARTG number:	130100, 177174, 177176, 206764 and 236039
, *Black Triangle Scheme*	No
Active ingredient:	Abatacept
Product name:	Orencia
Sponsor's name and address:	Bristol Myers Squibb Australia Pty Ltd. 4 Nexus Court, Mulgrave VIC 3170
Dose form:	Solution for subcutaneous injection Powder for intravenous infusion
Strength:	Solution 125 mg in 1 mL Powder 250 mg
Container:	Prefilled syringe (125 mg) Prefilled ClickJect autoinjector (125 mg) Vial (250 mg)
Pack size:	Prefilled syringe/ Prefilled ClickJect autoinjector: 4 Vial: 1
Approved therapeutic use:	*Orencia is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs.*
Route of administration:	Subcutaneous (SC) injection or intravenous (IV) infusion
Dosage:	For adult patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA), Orencia may be administered as an intravenous infusion or a subcutaneous injection. Methotrexate, other non-biologic disease modifying anti-rheumatic drugs (DMARD), corticosteroids, salicylates, non-steroidal anti-inflammatory drugs, or analgesics may be used during treatment with Orencia. *IV dosing regimen rheumatoid arthritis and psoriatic arthritis*

Orencia should be administered as a 30 minute intravenous infusion utilising the weight range based dosing (500 mg, 750 mg or 1 gram). Following the initial IV administration, an intravenous infusion should be given at 2 and 4 Weeks after the first infusion and every 4 weeks thereafter.

Subcutaneous dosing regimen psoriatic arthritis

Orencia should be administered weekly at a dose of 125 mg by subcutaneous injection without the need for an intravenous loading dose. Orencia can be used with or without non-biologic DMARDs. Patients switching from Orencia intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Product background

This AusPAR describes the application by the sponsor to register abatacept for the following additional indication:

> *Orencia is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs.*

Information on the conditions being treated

Psoriatic arthritis (PsA) is an inflammatory arthropathy associated with psoriasis, which is classified within the group of the spondyloarthritis. Psoriasis affects 1 to 3% of the population, with approximately a third of patients developing PsA which is usually diagnosed years after the appearance of psoriatic skin disease.

In about 67% of patients, psoriasis is present before the onset of the arthropathy, whereas in approximately 15% of patients the arthritis precedes the skin disease by more than one year. The reported prevalence of inflammatory arthritis in people with psoriasis varies widely from 6% up to 42%. The estimated prevalence of PsA ranges between 0.1% and 1%. PsA can develop at any time, but for most people it appears between the ages of 30 and 50, and affects men and women equally. PsA is associated with an increased risk of cardiovascular disease.

With the exception of the distal interphalangeal joints (hands and feet), there are no predictable joints for involvement in PsA and the signs of inflammation are often non symmetrical and more difficult to detect compared with rheumatoid arthritis (RA). Spondyloarthopathy is often present. Some typical features of PsA are dactylitis and nail psoriasis. Extra-cutaneous and extra-articular manifestations are uncommon but may include conjunctivitis, uveitis, aortic insufficiency and pulmonary fibrosis. Ocular inflammation most commonly presents as conjunctivitis, although up to 7% of patients can develop iritis.

PsA may start slowly with mild symptoms, or develop quickly. Flares and remissions usually characterise the course of PsA. Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, several physical limitations and disability. For most patients, skin manifestations predate the arthritis. Prognosis of PsA may range widely from a mild monoarthritic form with good prognosis to an erosive and destructive polyarticular form, comparable with that in patients with RA. Axial forms may also range from mild to severe and disabling. Because the severity of the psoriasis and the

arthritis may be discordant in PsA, there are patients with moderate or severe arthritis who have well-controlled or no, to minimal, psoriasis.

In most patients with PsA, the arthropathy affects peripheral joints alone and may present with dactylitis (inflammation of a single finger or toe) or enthesitis (inflammation at the sites of tendon and ligament attachment to bone). The following patterns of joint involvement are recognised:

- *Oligoarticular peripheral arthritis:* occurs in 50% of patients; involves up to five joints. Over time many of these patients will develop polyarticular disease.
- *Polyarticular peripheral arthritis*: occurs in 30% of patients; may resemble RA.
- *Predominant sacroiliitis and spondylitis:* occurs in up to 10% of patients.
- *Predominant distal interphalangeal joint involvement in both hands and feet:* occurs in 5% of patients.
- *Arthritis mutilans*: occurs in up to 5% of patients. It presents as osteolysis or dissolution of bone.

Within trials of apremilast, secukinumab, and ustekinumab, that analysed the tumour necrosis factor inhibitor (TNFi)-exposed and TNFi-naive subjects separately, the proportion of subjects achieving an ACR20 score;[1] was lower for TNFi exposed than in TNFi naive subjects. 40% to 60% of patients treated with current therapies, do not reach a minimal improvement in their joint disease (that is, ACR20) based on clinical trial data. It is not yet known what factors determine whether a patient will improve on a given therapy, and whether those factors are unique for different therapies. Thus, there is still need for therapies in PsA that offer a novel mechanism of action and can provide significant improvement in arthritis with an acceptable risk-benefit profile.

Drug class and therapeutic indication

Orencia (abatacept rch) belongs to the drug class of 'monoclonal antibodies.' Abatacept is a costimulation modulator of the interaction of CD80 and CD86 on antigen presenting cells with CD28 on T-lymphocytes. Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH_2, and CH_3 domains) portion of human immunoglobulin G1 (IgG1).

The proposed extension of indications is for the following:

> *Orencia is indicated for the treatment of active psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs.*

Orencia (abatacept) is currently registered for the following indications:

> *Orencia in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumour necrosis factor (TNF) blocking agents. A reduction*

[1] American College of Rheumatology (ACR) responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR20 response is defined as a ≥20% improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) ≥20% improvement in 3 of the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ and CRP. ACR50 and ACR70 are similarly defined.

in the progression of joint damage and improvement in physical function have been demonstrated during combination treatment with Orencia and methotrexate.

Orencia in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Orencia is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older, with moderately to severely active polyarticular juvenile idiopathic arthritis, who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Orencia may be used as monotherapy or concomitantly with methotrexate (MTX). (There is no clinical trial data for the use of Orencia subcutaneous formulation in children, therefore its use in children cannot be recommended.).

Current treatment options

Treatment includes physical therapy, patient education as well as medication. Mild PsA is generally treated with non-steroidal anti-inflammatory drugs (NSAIDs). When only few joints are involved, local injections of steroids might be effective. For extensive or severe PsA systemic conventional therapies such as methotrexate and sulfasalazin are standard therapies. Other products such as cyclosporine, antimalaric drugs and gold salts are also used, although there are limited data. Recently, drugs such as leflunomide and TNF-alpha antagonists have been used in treatment of PsA.

Skin involvement may vary from mild to a severe disease and skin activity is commonly not mirrored by arthritis activity. Topical medications for mild forms including corticosteroid creams, ultraviolet irradiation and vitamin D cream are commonly used. More severe disease requires ultraviolet A (UV A) irradiation plus psoralens, cyclosporine and methotrexate (MTX). Several new biological treatments have been recently approved for the treatment of resistant patients.

Some of the available drugs intended to treat arthritis might have an effect, positive or negative, on skin lesions.

TNFi agents were the first biologic agents approved for the treatment of PsA. Ustekinumab (Stelara) an inhibitor of IL-12/23, secukinumab, an antibody directed against IL-17 (Cosentyx) and apremilast (Otezla), an inhibitor of PDE4 were also recently approved for PsA.

Although oral MTX is a commonly used treatment in patients with PsA, efficacy for arthritis in subjects with PsA has not been definitively demonstrated. In the only randomised placebo controlled trial of MTX in patients with active PsA, oral MTX offered no advantage over placebo, as assessed by the Psoriatic Arthritis Response Criteria (PsARC), ACR20, and DAS28-CRP (Disease Activity Score – C-reactive protein);[2] responders.[3] This is in distinction to the large body of evidence supporting the efficacy of MTX in RA.[4] It is possible that MTX is less efficacious in PsA than RA due to the different immunologic mechanisms driving the diseases. For example, MTX may have a direct

[2] DAS = Disease activity score and DAS28 is a measure of the activity of rheumatoid arthritis. The DAS is based upon treatment decisions of rheumatologists in daily clinical practice.

[3] Kingsley GH, Kowalczyk A, Taylor H, et al. A randomised placebo controlled trial of methotrexate in psoriatic arthritis. Rheumatology 2012;51:1368-1377

[4] Favallia EG, Biggioggeroa M, Meronia PL. Methotrexate for the treatment of rheumatoid arthritis in the biologic era: Still an 'anchor' drug? Autoimmunity Reviews 2014;13:1102-1108

impact on autoantibody levels in RA[5] an effect that would not be relevant for PsA, which although T cell driven, like RA, does not have any autoantibody association.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 27 September 2007.

Orphan drug status

Not applicable.

International Regulatory Status

At the time the TGA considered this application a similar application had been approved in the United States of America (USA) and European Union (EU) and was under consideration in Canada as shown in Table 1.

Table 1: International regulatory status

Country Region Trade-name	Status Date	Indications
Canada Orencia	31 March 2017 Under review	Orencia is indicated for the treatment of adult patients with active psoriatic arthritis. Orencia can be used with or without non-biologic DMARDs.
EU Centralised Procedure Orencia	25 July 2017 Approved	Orencia, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy including MTX has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required.
USA Orencia	30 June 2017 Approved	Orencia is indicated for the treatment of adult patients with active psoriatic arthritis (PsA).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[5] Kastbom A, Forslind K, Ernestam S, et al. Changes in the anticitrullinated peptide antibody response in relation to therapeutic outcome in early rheumatoid arthritis: results from the SWEFOT trial. Ann Rheum Dis 2016;75:356-361

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for submission PM-2016-03491-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	3 January 2017
First round evaluation completed	31 May 2017
Sponsor provides responses on questions raised in first round evaluation	1 August 2017
Second round evaluation completed	15 September 2017
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	16 October 2017
Sponsor's pre-Advisory Committee meeting response	14 November 2017
Advisory Committee meeting	30 November to 1 December 2017
Registration decision	10 January 2018
Entry onto ARTG	12 January 2018
Number of TGA working days from submission dossier acceptance to registration decision *	208

*Statutory timeframe for standard applications is 255 working days

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type. The formulations used in the psoriatic arthritis clinical studies are the same as the approved IV and SC formulations for rheumatoid arthritis.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Clinical rationale

The approvals of new biologic therapies have greatly improved the management of patients with PsA. Unfortunately, 40% to 60% of patients treated with current therapies do not reach a minimal improvement in their joint disease (that is, ACR20) based on clinical trial data.[6],[7],[8],[9],[10],[11],[12] In addition, TNFi exposed patients may be more resistant to treatment, as the proportion of subjects achieving an ACR20 was lower for TNFi exposed than in TNFi naive subjects in trials of ustekinumab, apremilast and secukinumab.[13],[14] It is not yet known what factors determine whether a patient will improve on a given therapy, and whether those factors are unique for different therapies. Thus, there is still need for therapies in PsA that offer a novel mechanism of action and can provide significant improvement in arthritis with an acceptable risk-benefit profile. The need for additional therapies is particularly relevant for those patients who have failed to respond to a TNFi.[15]

Abatacept (Orencia) is a selective co-stimulation modulator that binds to CD80 and CD86 on antigen presenting cells, thereby blocking CD80/86 interaction with T-cell expressed CD28. The binding of CD80/86 to CD28 provides a co-stimulatory signal necessary for full activation of T-cells. PsA is associated with specific major histocompatibility complex class I genes (for example, human leukocyte antigen B*08:01, B*27:05, C*06:02, B*39:01, and B*38:01) 26 that code for molecules that are involved in antigen presentation to T-cells. There is strong non-clinical experimental evidence of T-cell involvement in PsA, which led to the evaluation of abatacept in the treatment of this disease.[16],[17],[18]

[6] Mease P, Goffe B, Metz, J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385-390
[7] Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50:2264-22
[8] Mease P, Gladman D, Ritchlin C, et al. Adalimumab for the treatment of patients with moderately to sevRitchlin, 2005; erly active psoriatic arthritis. Arthritis and Rheum 2005;52:3279-3289
[9] Genovese M, Mease P, Thomson G, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol 2007;34:1040-1050
[10] Antoni C, Kavanaugh A, Kirkham B, et al. Sustained benefits in infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis. Results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). Arthritis and Rheum 2005;52:1227-1236
[11] Antoni C, Kavanaugh A, Heijde D, et al. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol 2008;35:869-876
[12] Kavanaugh A, Heidje D, McInnes D, et al. Golimumab in psoriatic arthritis: One year clinical, efficacy, radiographic, and safety results from a Phase III, randomized placebo-controlled trial. Arthritis Rheum 2012:64:2504-2517
[13] Gottlieb A and Narang K. Ustekinumab in the treatment of psoriatic arthritis: latest findings and clinical potential. Ther Adv Musculoskelet Dis 2013;5:277–285
[14] Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis 2014;73:1020-1026
[15] McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human antiinterleukin- 17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double blind, placebo-controlled, phase 3 trial. Lancet 2015;386:1137-1146
[16] Ritchlin C. Pathogenesis of psoriatic arthritis. Current Opinions in Rheumatology 2005;17:406-412
[17] Prinz J. Which T cells cause psoriasis? Clin Exp Dermatol 1999;24:291-295
[18] Van Kujik AWR, Reinders-Blankert P, Smeets TJM, et al. Dtailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: implications for treatment. Ann Rheum Dis 2006;65:1551-1557

Guidance

The abatacept development program generally complies with the European Medicines Agency (EMA) Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis contents of the clinical dossier.[19]

Contents of the clinical dossier

Scope of the clinical dossier

The following clinical studies were submitted:

- Clinical pharmacology studies providing PK, PD and safety pharmacology data: No new dedicated Phase I PK/PD studies were included as part of the present submission. However, two new studies (Studies IM101158, and IM101332), which were Phase IIb and Phase III studies, respectively, both examined trough levels of abatacept, the attainment of steady-state in patients with PsA and the development of anti-drug antibodies for abatacept.
- Dose-finding studies: Phase IIb Study IM101158
- Population PK (popPK) analyses: a report provides population pharmacokinetic (popPK) and exposure-response (exposure-response) analyses for abatacept in patients with PsA in part based on the results from the two new studies. As part of the present submission the sponsor has also included a previously reviewed report, which examined the exposure-response relationship in patients with RA.
- Pivotal efficacy/safety studies: Study IM101332 was a placebo controlled Phase III study of abatacept administered via SC injection for the treatment of patients with active PsA. This study consists of a short term, 6 month, double blind period followed by a 6 month open label period, and then a 1 year long term extension of the open label period (for the collection of safety data only).
- Other efficacy/safety studies: Study IM101158 was a Phase IIb study that consisted of a short term, 6 month, double blind period in which the efficacy of three different IV regimens of abatacept (30/10 mg/kg, 10/10 mg/kg, or 3/3 mg/kg) was compared to placebo; subjects who completed the short term period received open label 10 mg/kg abatacept IV in the long term period, with a mean treatment duration of 17.8 months.
- Literature references: 43 references.

Paediatric data

Not applicable.

Good clinical practice

All clinical studies were conducted and reported according to Good Clinical Practice (GCP) guidelines. The studies were performed to meet the ethical requirements of Directive 2001/20/EC. The protocols, amendments, administrative letters, and subject informed consent forms received Institutional Review Board/Independent Ethics Committee approval/favourable opinion prior to implementation.

[19] European Medicines Agency Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 describes the pharmacokinetic (PK) studies submitted.

Table 3: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
Special Populations	Patients with PsA§	IM101158	To examine the PKs of each of the three abatacept treatment arms and the incidence of a positive immunogenicity response during the short term and long term periods.
		IM101332	To determine the time required for attainment of abatacept steady-state; the relationship between abatacept exposure and ADAs; and the incidence of immunogenicity.
PopPK analyses	Target population§	930102576	PopPK and exposure-response analysis for abatacept in patients with RA and PsA
	Other	930012830	Exposure-response analysis in patients with RA

* Indicates the primary PK aim of the study; § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

No new studies contained in the present submission examined the PK of abatacept in healthy subjects. Therefore, the following discussion pertains to the PK of abatacept in patients with PsA or RA only.

- For the treatment of PsA, abatacept is to be administered via either IV infusion or SC injection.
- The estimated absorption rate constant (k_a) of abatacept in patients with RA or PsA is 0.0025 L/h.
- The absolute bioavailability of the SC formulation of abatacept relative to the IV form has been previously reported to be 78.6%.
- Following either 10 mg/kg IV doses every four weeks or weekly doses of 125 mg SC, the trough plasma concentration (C_{min}) values at steady state were similar and steady-state was attained by Day 57 for both dosing regimens.
- The mean C_{min} values for abatacept following IV dosing were dose related.
- The steady-state C_{min} values following doses of both 10 mg/kg IV given monthly or 125 mg SC given weekly resulted in abatacept concentrations >10 µg/mL which are associated with the therapeutic efficacy of abatacept in patients with RA.
- The estimated central volume (VC), peripheral volume (VP), inter-compartmental clearance (Q) and clearance (CL) values were 3.2 L, 4.0 L, 0.025 L/h and 0.020 L/h, respectively.

- The inter-individual variability on CL, VC, VP, Q and k_a (absorption rate constant) were estimated to be 0.094, 0.067, 0.36, 0.43 and 1.9, respectively. Estimates for the proportional and additive residual errors were 0.056 and 0.15.
- Abatacept pharmacokinetic data, from a combination of RA and PsA patients, was best described by a linear two compartment popPK model with zero order IV infusion, first-order absorption of SC abatacept and first order elimination. Abatacept clearance increased with baseline body weight, baseline calculated glomerular filtration rate and baseline swollen joint count, whereas, it decreased with age and albumin and was lower in females and PsA patients. Clearance was also higher in patients receiving concomitant NSAIDs.
- Consistent with previous results in RA patients, popPK analyses for abatacept in PsA patients identified that there was a trend toward higher abatacept clearance as body weight increased. In addition, relative to the RA patients with the same body weight, abatacept clearance in PsA patients was approximately 8% lower, resulting in slightly higher abatacept peak steady state plasma levels ($C_{max,ss}$) and mean steady state plasma levels ($C_{av,ss}$) but not steady state trough concentration ($C_{min,ss}$) values in patients with PsA. Given the magnitude of the difference in CL between the two diseases and the exposure-response analyses identifying $C_{min,ss}$ as the best exposure measure for predicting pharmacodynamics responses (as discussed in the following sections of this report), this difference is unlikely to be clinically significant.

The PK information in the proposed PI and Consumer Medicine Information (CMI) is satisfactory.

Pharmacodynamics

Studies providing pharmacodynamic data

All of the new studies included in the submission that contained pharmacodynamic results also contained PK data and therefore have been summarised in Table 3 above.

Evaluator's conclusions on pharmacodynamics

- Abatacept is a human CTLA-4-Ig fusion protein that inhibits T-cell activation by blocking CD28-mediated co-stimulation.
- In patients with PsA, immunogenicity rates following administration of IV or SC abatacept were low. For instance, following 10 mg/kg IV dosing every 4 weeks or weekly SC doses of 125 mg, 0% and 3.9% of patients, respectively, were identified as screening positive for anti-drug antibodies (ADAs). In addition, for the SC population, for which we have data, immunogenicity rates were similar in patients who received active drug (3.9% positive for ADAs) and those receiving placebo (8.6%).
- Pharmacometric analyses of data taken from a mixed population of patients with RA or PsA identified that there were significant relationships between abatacept exposure (based on steady state trough concentration $C_{min,ss}$) and the efficacy endpoints, ACR20, ACR50, ACR70, PASI50;[20] PASI75 and DAS28-CRP, whereby increases in abatacept exposure were positively correlated with efficacy response.

[20] Psoriasis Area and Severity Index (PASI): Total PASI scores were calculated by multiplying the area of involvement score, the sum of the severity scores for erythema, induration, and scaling, and a weight factor for that body area (0.1, 0.2, 0.3, and 0.4 for head, upper extremities, trunk, and lower extremities, respectively), and then summing across all 4 body areas. The total range of the PASI score is 0 to 72, where 0 = no psoriasis and 72 = severe disease.

- Stochastic simulations predicted that following administration of either 125 mg SC or 10 mg/kg IV, steady-state trough concentrations of 11.8 µg/mL and 8.5 µg/mL or higher, would be attained in 95% of PsA patients, respectively, regardless of body weight.
- Graphical analysis of the relationship between steady-state exposures and adverse events (AEs) showed no clear association between abatacept exposure and safety.
- Overall the results indicate that both weekly SC administration of 125 mg abatacept or 10 mg/kg IV dosing every four weeks result in similar and effective improvements in ACR20 and PASI50 scores at 6 months. By contrast, the response provided by 3 mg/kg IV abatacept administered every 4 weeks was not as beneficial.
- An analysis of data obtained from a population of patients with RA only, also indicated that there was a relationship between ACR20 response and abatacept exposure.

Dosage selection for the pivotal studies

Study IM101158 was a Phase II study and the first study conducted with abatacept in PsA patients which used the IV formulation of abatacept. Study IM101158 was a Phase IIb study that consisted of a short term, 6 month, double blind period in which the efficacy of three different IV regimens of abatacept (30/10 mg/kg, 10/10 mg/kg, or 3/3 mg/kg) was compared to placebo, as measured by ACR20 responses at Day 169 (Week 24). Subjects who completed the short term period received open label 10 mg/kg abatacept IV in the long term period, with mean treatment duration of 17.8 months.

Evaluator's conclusions on dose finding for the pivotal studies

Based on the therapeutic equivalence of 125 mg SC weekly to 10/10 mg/kg IV monthly dose of abatacept in RA (for example, Study IM1011741), and the comparison of pharmacokinetic results to the IV formulation in PsA in Study IM01158, a fixed-dose, 125 mg weekly SC abatacept regimen was selected for use in Study IM101332.
Study IM101158 established a dose-response relationship for IV abatacept treatment in both TNFi-naive and TNFi-exposed subjects with PsA. Although interpretation was limited by small numbers and the fact that randomisation to treatment groups was not stratified by prior TNFi use.

Based on the therapeutic equivalence of abatacept in RA and the analysis of exposures with IV abatacept across RA and PsA (for example, Study IM101174 and Study IM101158), a fixed-dose, 125 mg weekly SC abatacept regimen was selected for studying the efficacy and safety in subjects with PsA in this trial. Abatacept SC was administered without an IV loading dose in the pivotal Phase III Study IM101332.

The proposed IV abatacept dose of 10 mg/kg was only evaluated in 40 subjects in the Phase IIb dose-ranging Study IM101158. No Phase III study was conducted with the proposed IV abatacept dose.

Efficacy

Studies providing efficacy data

- Study IM101332: A Phase III randomised placebo controlled study to evaluate the efficacy and safety of abatacept subcutaneous injection in adults with active psoriatic arthritis.

- Study IM101158: A Phase IIb, multi-dose, multi-centre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of abatacept versus placebo in the treatment of psoriatic arthritis.

Study IM101332 was a pivotal 24 week (168 day), Phase III, randomised, double blind, placebo controlled study, followed by a 28 week (196 day) open label period and a 1 year long term extension period (for collection of safety data only) of abatacept (125 mg SC every week) in subjects with active PsA. This study included subjects who had an inadequate response and/or intolerance to non-biologic DMARDs and may or may not have been exposed to TNFi therapy. The parameters used to assess the efficacy of abatacept in this study were consistent with other studies of therapeutic agents in a population with PsA and generally complied with the EU guidelines for investigation of therapeutic agents for psoriatic arthritis related double blind related.

Evaluator's conclusions on efficacy

The efficacy and safety of Orencia were assessed in 594 adult patients with active PsA in two randomised, double blind, placebo controlled trials. Patients had active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior treatment with DMARD therapy and had one qualifying psoriatic skin lesion of at least 2 cm in diameter. The Phase IIb Study IM101158 evaluated efficacy of three IV abatacept dosing regiments (30/10, 10/10 and 3/3 mg/kg) in 170 patients while the pivotal Phase III Study IM101332 evaluated efficacy/safety of weekly administration of abatacept 125mg SC in 424 patients. The studies were well-conducted and generally complied with EU guidelines on investigation of medicinal products for treatment of PsA. However, the clinical study reports for both studies did not specify if patients with each type of PsA (polyarticular arthritis; spondylitis with peripheral arthritis; asymmetric peripheral arthritis, distal interphalangeal involvement) were enrolled in the study.

Joint signs and symptoms

Abatacept, administered SC or IV, was more effective than placebo in reducing the joint signs and symptoms in subjects with PsA. The pivotal Study IM101332 met its primary endpoint, demonstrating that treatment with abatacept SC (125 mg weekly without IV loading dose) compared with placebo (39.4% versus 22.3%) resulted in a statistically significantly higher proportion of subjects achieving an ACR20 response at Day 169. In Study IM101158, the primary efficacy endpoint was achieved for the abatacept IV 30/10 and 10/10 mg/kg treatment groups, but not for the abatacept 3/3 mg/kg group (42%, 48%, 33% and 19% in abatacept 30/10, 10/10, 3/3 mg/kg and placebo groups, respectively). Responses in the 30/10 and 10/10 mg/kg IV groups were similar, suggesting no added benefit of the 2 loading doses of 30 mg/kg IV.

A numerically higher proportion of subjects, both among those who were TNF inhibitor (TNFi) naive and who were TNFi exposed, achieved an ACR20 response in the abatacept group compared with the placebo group in the two studies. However, only post hoc analysis (based on prior TNFi use) was done in the Phase IIb study and in the Phase III pivotal study, the first key secondary endpoint (Health assessment questionnaire, HAQ) failed to show statistically significant difference between abatacept and placebo groups, limiting interpretation of observed results for the subsequent key secondary endpoints in the pre-specified hierarchical approach (ACR20 responders in TNFi-naïve/exposed subjects and proportion of radiographic non-progressors).

In Study IM101332, a numerically higher proportion of subjects in the abatacept group, compared with the placebo group, met the criteria for an ACR50 (19.2% versus 12.3%) and ACR70 (10.3% versus 6.6%) response at Day 169; Study IM101158 showed similar results with IV abatacept with highest responses observed with proposed dose of 10/10 mg/kg (ACR50 = 20.9%, 25%, 15.6% and 2.4% in abatacept 30/10, 10/10,

3/3 mg/kg and placebo groups, respectively; ACR70 = 4.7%, 12.5%, 8.9% and 0%, respectively). The proportions were higher in the abatacept groups than in the placebo group in both TNFi-naive and TNFi-exposed subjects (in both ACR50 and ACR70 for Study IM101332 and in ACR50 for Study IM101158).

Abatacept efficacy on the arthritis of PsA was supported by greater improvements in the mean change from baseline in the DAS28-CRP scores in both studies.

Physical function

The HAQ response was numerically better in the abatacept groups compared with the placebo groups across both studies. In Study IM101332, although the proportion of subjects with HAQ response (decrease of at least 0.35, considered to be the current definition of minimally clinically important difference (MCID) for Health Assessment Questionnaire Disability Index (HAQDI) in PsA) at Day 169 in Study IM101332 was numerically higher in the abatacept group than the placebo group, the difference was not statistically significant (33% versus 23.7%). In Study IM101158, the proportion of subjects with an improvement in physical function at Day 169, defined as at least a 0.3 unit improvement from baseline in the HAQDI score (earlier definition of MCID in PsA), was numerically higher for all three abatacept groups (34.9% to 45.0%) than for the placebo group (19.0%) with the largest difference observed for the abatacept 10/10 mg/kg group.

Structural changes through imaging

Although difficult to definitively demonstrate in a 6 month placebo controlled trial, abatacept treatment compared with placebo inhibited synovitis, bone oedema, and erosion as assessed by MRI in Study IM101158 (exploratory endpoint) and resulted in fewer subjects with radiographic progression of x-rays in Study IM101332 (key secondary endpoint). In the pivotal Phase III study, treatment with abatacept SC was associated with a larger proportion of subjects being radiographic non-progressors, defined as a change from baseline in total PsA modified Sharpe/van der Heijde score (SHS) < 0, at Day 169 compared with placebo (42.7% versus 32.7%, p = 0.034). Assessment of structural changes by X-rays up to Year 1 tend to suggest that most subjects did not progress once abatacept treatment was started during the open label and that changes in PsA-modified SHS total score, erosion score and joint space narrowing (JSN) score were lower in the group that had received abatacept since baseline compared to the group that had received 4 to 6 months of placebo initially although interpretation was limited by 95% confidence intervals which were wide and overlapping between the two treatment groups (see Tables 4 to 7, below).

Table 4: Radiographic non-progressors (missing X-rays imputed as progressors)

		Abatacept SC (N=213)	Placebo (N=211)
Total SHS Score Change from Day 169 <=0	Number of subjects n/m (%) 95% CI	121/179 (67.6%) (60.7, 74.5)	121/169 (71.6%) (64.8, 78.4)
Erosion Score Change from Day 169 <=0	Number of subjects n/m (%) 95% CI	125/179 (69.8%) (63.1, 76.6)	126/169 (74.6%) (68.0, 81.1)
Joint Space Narrowing Change from Day 169 <=0 Score	Number of subjects n/m (%) 95% CI	135/179 (75.4%) (69.1, 81.7)	130/169 (76.9%) (70.6, 83.3)

PsA-modified Sharp/Van der Heijde Scoring.
n = Number of subjects without progression, m = Number of subjects with baseline (Day 169 or Day 57 OL for early escape subjects).
Baseline= Day 169 (or Day 57 OL for early escape subjects)
For early escape subjects, the Day 365 x-ray is performed at Day 309 (Day 197 OL).

				Abatacept SC	Placebo
Day 169	Total SHS Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	142/180 (78.9%) (72.9, 84.9)	135/173 (78.0%) (71.9, 84.2)
Day 365	Total SHS Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	112/148 (75.7%) (68.8, 82.6)	115/152 (75.7%) (68.8, 82.5)
Day 169	Erosion Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	149/179 (83.2%) (77.8, 88.7)	145/173 (83.8%) (78.3, 89.3)
Day 365	Erosion Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	119/148 (80.4%) (74.0, 86.8)	124/152 (81.6%) (75.4, 87.7)
Day 169	Joint Space Narrowing Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	157/182 (86.3%) (81.3, 91.3)	151/175 (86.3%) (81.2, 91.4)
Day 365	Joint Space Narrowing Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	129/148 (87.2%) (81.8, 92.6)	129/152 (84.9%) (79.2, 90.6)

PsA-modified Sharp/Van der Heijde Scoring.
n = Number of Non-progressors, m = Number of subjects in the analysis.
For early escape subjects, the Day 169 x-ray is performed at Day 57 OL and Day 365 x-ray at Day 309 (Day 197 OL).
For subjects with missing data at Day 169 and measurements at Day 365, if subject is a non-progressor at Day 365 (Day 309 for Early Escape) then missing Day 169 is imputed as a non-progressor

Table 5: Radiographic non-progressors; analysis using actual values

				Abatacept SC	Placebo
Day 169	Total SHS Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	142/180 (78.9%) (72.9, 84.9)	135/173 (78.0%) (71.9, 84.2)
Day 365	Total SHS Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	112/148 (75.7%) (68.8, 82.6)	115/152 (75.7%) (68.8, 82.5)
Day 169	Erosion Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	149/179 (83.2%) (77.8, 88.7)	145/173 (83.8%) (78.3, 89.3)
Day 365	Erosion Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	119/148 (80.4%) (74.0, 86.8)	124/152 (81.6%) (75.4, 87.7)
Day 169	Joint Space Narrowing Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	157/182 (86.3%) (81.3, 91.3)	151/175 (86.3%) (81.2, 91.4)
Day 365	Joint Space Narrowing Score	Change from Baseline <=0	Number of subjects n/m (%) 95% CI	129/148 (87.2%) (81.8, 92.6)	129/152 (84.9%) (79.2, 90.6)

PsA-modified Sharp/Van der Heijde Scoring.
n = Number of Non-progressors, m = Number of subjects in the analysis.
For early escape subjects, the Day 169 x-ray is performed at Day 57 OL and Day 365 x-ray at Day 309 (Day 197 OL).
For subjects with missing data at Day 169 and measurements at Day 365, if subject is a non-progressor at Day 365 (Day 309 for Early Escape) then missing Day 169 is imputed as a non-progressor

Table 6: Proportion of non-progressors in total SHS, erosion and JSN score over time (Day 169 and Day 365) by prior TNF use; analysis using actual values

					Abatacept SC	Placebo
No Prior TNF	Day 169	Total SHS Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	56/73 (76.7%) (67.0, 86.4)	57/72 (79.2%) (69.8, 88.5)
	Day 365	Total SHS Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	51/73 (69.9%) (59.3, 80.4)	52/72 (72.2%) (61.9, 82.6)
	Day 169	Erosion Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	60/73 (82.2%) (73.4, 91.0)	61/72 (84.7%) (76.4, 93.0)
	Day 365	Erosion Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	56/73 (76.7%) (67.0, 86.4)	56/72 (77.8%) (68.2, 87.4)
	Day 169	Joint Space Narrowing Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	60/73 (82.2%) (73.4, 91.0)	63/72 (87.5%) (79.9, 95.1)
	Day 365	Joint Space Narrowing Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	55/73 (75.3%) (65.5, 85.2)	55/72 (76.4%) (66.6, 86.2)
Prior TNF	Day 169	Total SHS Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	82/108 (75.9%) (67.9, 84.0)	79/102 (77.5%) (69.3, 85.6)
	Day 365	Total SHS Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	58/108 (53.7%) (44.3, 63.1)	60/102 (58.8%) (49.3, 68.4)
	Day 169	Erosion Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	86/108 (79.6%) (72.0, 87.2)	85/102 (83.3%) (76.1, 90.6)
	Day 365	Erosion Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	60/108 (55.6%) (46.2, 64.9)	65/102 (63.7%) (54.4, 73.1)
Prior TNF						
	Day 169	Joint Space Narrowing Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	92/108 (85.2%) (78.5, 91.9)	84/102 (82.4%) (75.0, 89.8)
	Day 365	Joint Space Narrowing Score	Change from Baseline (Day 1) <=0	Number of subjects n/m (%) 95% CI	70/108 (64.8%) (55.8, 73.8)	67/102 (65.7%) (56.5, 74.9)

PsA-modified Sharp/Van der Heijde Scoring.
n = Number of Non-progressors, m = Number of subjects in the analysis.
For Early Escape subjects, the Day169 x-ray is performed at Day 57 CL and Day 365 x-ray at Day 309 (Day 197 CL).
For subjects with missing data at Day 169 and measurements at Day 365, if subject is a non-progressor at Day 365 (Day 309 for Early Escape) then missing Day 169 is imputed as a non-progressor

Table 7: Adjusted mean change from Baseline at Day 365 in total SHS, erosion and JSN score; Intention to treat population

Study Day		Abatacept SC (N=213)	Placebo (N=211)
Day 365	Total SHS Score		
	n	206	202
	Baseline Mean (SD)	18.79 (45.416)	17.02 (40.415)
	Post-Baseline Mean (SD)	19.15 (45.524)	17.48 (40.740)
	Median Change from Baseline (25%, 75%, 90%, 95%)	0.00 (0.00, 0.50, 1.12, 2.00)	0.00 (0.00, 0.50, 1.16, 2.00)
	Unadjusted Change from Baseline (SD)	0.36 (1.116)	0.46 (1.590)
	Adjusted Change from Baseline (SE)	0.25 (0.119)	0.36 (0.121)
	95% CI	(0.02, 0.49)	(0.12, 0.59)
Day 365	Erosion Score		
	n	206	202
	Baseline Mean (SD)	10.87 (26.129)	9.35 (21.904)
	Post-Baseline Mean (SD)	11.08 (26.197)	9.57 (22.078)
	Median Change from Baseline (25%, 75%, 90%, 95%)	0.00 (0.00, 0.44, 0.76, 1.39)	0.00 (0.00, 0.27, 0.55, 1.00)
	Unadjusted Change from Baseline (SD)	0.21 (0.723)	0.22 (0.713)
	Adjusted Change from Baseline (SE)	0.16 (0.064)	0.18 (0.065)
	95% CI	(0.04, 0.29)	(0.05, 0.31)
Day 365	Joint Space Narrowing Score		
	n	206	202
	Baseline Mean (SD)	7.92 (19.609)	7.67 (19.046)
	Post-Baseline Mean (SD)	8.11 (19.627)	7.96 (19.205)
	Median Change from Baseline (25%, 75%, 90%, 95%)	0.00 (0.00, 0.36, 0.74, 1.00)	0.00 (0.00, 0.47, 0.94, 1.50)
	Unadjusted Change from Baseline (SD)	0.19 (0.645)	0.29 (1.100)
	Adjusted Change from Baseline (SE)	0.14 (0.076)	0.24 (0.077)
	95% CI	(-0.01, 0.29)	(0.09, 0.39)

Change from Baseline = Post-baseline - Baseline value.
n is the number of subjects with both post-baseline and baseline measurements (after MI).
For Early Escape Subjects the observed measurements at Day 169 (Day 57 of open-label) and Day 365 (Day 197 of open-label) are used in the analysis.
Missing values at Day 169 and at Day 365 are imputed via multiple imputation (Proc MI in SAS) applying the monotone regression model with variables treatment, prior TNFi use, MTX use and BSA (as class variables), baseline score, score at Day 169 and score at Day 365. After imputation, a longitudinal repeated measures analysis is performed with fixed categorical effects of treatment, day, prior TNF use, MTX use, BSA, day-by-treatment interaction, prior TNF-use-by-day interaction, MTX use-by-day interaction, BSA-by-day interaction as well as the continuous fixed covariate of baseline score and baseline score-by-day interaction. An unstructured covariance matrix is used to represent the correlation of the repeated measures within each subject.

The effect of abatacept treatment on structural damage in PsA was not evaluated beyond 1 year. It is important to note that according to EU guidelines for medicinal products for treatment of PsA, '*slowing of radiographic progression may itself not constitute a definite patient benefit and it is still not accepted surrogate for long term clinical benefit. Furthermore, confirmatory trials for prevention of structural damage require an observation period of at least 2 years showing that sustained benefits are maintained after the first year*.' Hence, evidence to support prevention of structural damage with abatacept in treatment of PsA is not considered adequate.

Additional musculoskeletal changes

In contrast to RA, patients with PsA usually present with musculoskeletal inflammation and pain in addition to peripheral joint arthritis, including enthesitis, dactylitis, and spine arthritis. Additional measures of musculoskeletal changes were analysed in the short term Period for each study. In Study IM101332, there were greater improvements in enthesitis (LEI, Leeds Enthesitis Index) and dactylitis (by both the LDI (Leeds Dactylitis Index) and a dactylitic digit count) from Baseline to Day 169 in the abatacept group compared with the placebo group. In Study IM101158, larger adjusted mean reductions from baseline were observed in all three abatacept groups compared with placebo at each scheduled assessment from Day 15 through Day 169 for dactylitis, and from Day 57 through Day 169 for enthesitis.

Psoriasis

In both studies during the controlled period, topical therapies were only permitted to be used on sensitive areas (for example, face, palms, soles, and intertriginous areas) and never on the target lesion being assessed. In Study IM101332, the proportion of subjects who achieved at least 50% improvement in PASI50 scores at Day 169 was numerically higher in the abatacept group than in the placebo group (26.7% versus 19.6%) with slightly better efficacy observed in TNFi naïve (32.7% versus 19.6%) compared with TNFi exposed subjects (23.1% versus 19.6%). Similar results were observed for patients who achieved at least 75% improvement in PASI75 at Day 169. The proportion of subjects who achieved PASI50 or 75 was numerically greater in subjects in the abatacept group than in the placebo group, regardless of methotrexate use or use of any DMARD. In Study IM101158, a larger proportion of subjects in the three abatacept groups, compared with placebo, achieved PASI50 and PASI75. It is important to note that the greatest benefit in psoriasis in this study was seen in the 3 mg/kg group and the long term period of this study was prematurely terminated due to the modest efficacy on skin related parameters.

Overall, abatacept treatment was associated with modest improvement in psoriasis in terms of PASI50 and PASI75 response rates. Although, no new forms of psoriasis developed in response to abatacept treatment in the controlled periods of the two studies, abatacept (SC and IV) was associated with modest improvements in psoriasis with no statistically significant improvements in any of the assessed skin efficacy endpoints.

Composite measures

Composite measures of musculoskeletal and skin changes, including modified psoriatic disease index (mCPDAI), psoriatic arthritis disease activity score (PASDAS), and minimal disease activity (MDA) were analysed in Study IM101332. There were numerically greater improvements in the mCPDAI and the PASDAS in the abatacept group compared with the placebo group at Day 169. Minimal disease activity is a composite measure that defines remission in PsA and a numerically higher proportion of subjects achieved minimal disease activity in the abatacept group (11.7%) compared with the placebo group (8.1%) at Day 169.

Health related Quality of Life (QOL)

In Study IM101332, subjects in the abatacept group reported greater mean improvements from Baseline to Day 169 in the physical component summary (PCS) score of the SF-36;[21] than subjects in the placebo group. Changes in the mental component summary (MCS) were similar in both groups. In all three abatacept IV treatment groups in Study IM101158, the adjusted mean changes from baseline at Day 169 in SF-36 physical component summary and mental component summary scores were greater than 3 points for both SF-36 component scores.

Long term efficacy results from completed Phase IIb Study IM101158 and pivotal Study IM101332 (up to 1 year-end of open label phase)

Joint signs and symptoms

During the open label phase Study IM101332, the treatment benefits in terms of ACR20 observed in the abatacept group were maintained from the 6 month assessment through the 1 year assessment, and improvements were seen in the placebo group upon switching to open label abatacept at Day 113 or at Day 169. These benefits were seen in both TNFi naive and TNFi-exposed subgroups of subjects. Continued improvements were also seen in the DAS28-CRP over time. In Study IM101158, the improvements in ACR20 rates that were evident in the abatacept 30/10 and 10/10 mg/kg groups at the end of the short term period were maintained during continued treatment with abatacept 10 mg/kg in the long term period for up to Day 897 (Month 30 of study). ACR20 rates for subjects in the short term placebo and abatacept 3/3 mg/kg cohorts tended to increase when these subjects were switched to treatment with abatacept 10 mg/kg during the long term period.

Physical function

The proportion of subjects with HAQ responses was maintained over time in the abatacept groups and improved in the placebo groups after switching to abatacept in both studies.

Structural changes

In Study IM101332, regardless of the original randomisation group, most subjects did not progress once abatacept treatment was started during the open label period. In Study IM101158, reductions in bone oedema and synovitis were observed at Day 365 in the randomised placebo cohort after the start of abatacept treatment and was maintained in the abatacept 30/10 and 10/10 mg/kg cohorts. However, prevention of structural damage with abatacept treatment in PsA was not evaluated beyond one year.

Additional musculoskeletal changes

In Study IM101332, the adjusted mean change in the Leeds enthesitis index (LEI), Leeds dactylitis index (LDI), and number of dactylitic digits continued to improve during the open label period for both the abatacept treatment group and the placebo group after receiving treatment with abatacept. The proportion of subjects with dactylitis at baseline with no dactylic digits at Day 365 was 68.9% and 60.0% in the abatacept/abatacept and placebo/abatacept group, respectively, and the proportion of subjects with enthesitis at baseline with no enthesitis at Day 365 was 48.6% and 43.9% in the abatacept/abatacept and placebo/abatacept group, respectively. The adjusted mean change in the Bath

[21] **The SF-36** is a multi-purpose, short-form health survey with only 36 questions. It yields an 8 scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4 week recall) and acute (1 week recall).

Ankylosing Spondylitis Disease Activity Index (BASDAI) improved during the open label period for subjects who remained on abatacept and for subjects who transitioned to abatacept at Days 113 or 169.

Psoriasis

In Study IM101332, the treatment benefits on PASI50 or 75 responses observed in the abatacept group were maintained from the 6 month assessment through the 1 year (Day 309) assessment, and improvements were seen in the placebo group upon switching to open label abatacept. In Study IM101158, the proportion of subjects with a 50% or 75% improvement from baseline in the PASI score (PASI50 or PASI75) was variable and the long term phase of this study was discontinued due to modest efficacy on skin manifestations in patients with PsA.

Composite measures

The mCPDAI and PASDAS decreased during the open label period for the subjects who continued to receive abatacept and for placebo subjects who transitioned to abatacept on Day 113 or 169 improvements in mCPDAI and the PASDAS were similar in the abatacept and placebo groups at Day 365. The proportion of subjects who achieved MDA increased over time to Year 1 in the abatacept group and in the placebo group after switching to abatacept at Day 113 or at Day 169. By Day 365, 17.4% of subjects continuing on the abatacept regimen and 18.5% of subjects on the placebo/abatacept regimen had achieved the stringent MDA definition of remission.

Health related quality of life

In Study IM101332, PCS and MCS scores of the SF-36 improved during the open label period for the subjects who continued on abatacept and for those who transitioned from placebo to abatacept at Day 113 or 169. For all subjects in Study IM101158, the mean changes from baseline in the physical and mental component summary scores (PCS and MCS) of the SF-36 were generally maintained or improved upon switching to open label abatacept 10 mg/kg during the long term period.

Limitations

- Efficacy of proposed IV dosing with 10 mg/kg was not evaluated in a Phase III study; it was only evaluated in the Phase IIb Study IM101158 which was also the first study of abatacept in patients with PsA and only 40 subjects were treated with proposed IV abatacept dose of 10 mg/kg in the double blind controlled phase.
- Efficacy of abatacept IV in subgroups based on prior TNFi use was only done in a post hoc analysis in Phase IIb study which was also limited as randomised patients were not stratified by prior TNFi use. In Phase III study, the first key secondary endpoint (HAQ) failed to show statistically significant difference between abatacept and placebo groups, limiting interpretation of observed results for the subsequent key secondary endpoints in the pre-specified hierarchical approach (ACR20 responders in TNFi-naïve/exposed subjects and proportion of radiographic non-progressors).
- The Phase III study evaluating weekly treatment with 125 mg abatacept SC showed non-significant modest improvements in all psoriasis endpoints (PASI50, PASI75, Target lesion 50% improvement (TL50), Target lesion 75% improvement (TL75)) compared with placebo. The Phase IIb Study IM101158 showed numerically greater benefit with the 3/3 mg IV dose while the proposed 10/10 mg/kg dose only showed minimal efficacy. Furthermore, the long term phase of the Phase IIb study was terminated early due to modest efficacy on skin related parameters.

Safety

Studies providing safety data

- Study IM101332 was a placebo controlled Phase III study of abatacept administered via SC injection for the treatment of patients with active PsA. This study consists of a short term, 6 month, double blind period followed by a 6 month open label Period, and then a 1 year long term extension of the open label period (for the collection of safety data only).
- Study IM101158 was a Phase IIb study that consisted of a short term, 6 month, double blind period in which the efficacy of three different IV regimens of abatacept (30/10 mg/kg, 10/10 mg/kg, or 3/3 mg/kg) was compared to placebo; subjects who completed the short term period received open label 10 mg/kg abatacept IV in the long term period, with a mean treatment duration of 17.8 months.

Patient exposure

Study IM101332 provided safety data for short term (for the abatacept and placebo groups), and for the cumulative abatacept period up to Year 1 and up to Year 2 (includes all subjects who received at least 1 dose of abatacept); this study is ongoing and the safety data for the cumulative abatacept period up to Year 2 are considered interim as the data cut off (last patient last visit (LPLV)) was 22 January 2016. In Study IM101332, during the short term period, the mean duration of exposure to study drug was similar in the abatacept and placebo groups: 147.7 and 140.3 days, respectively. A total of 46% (n = 98) of subjects in the abatacept group and 36% (n = 76) of subjects in the placebo group were exposed to study drug for < 141 to 169 days (see Table 8).

A total of 35.7% of subjects in the abatacept group and 42.2% of subjects in the placebo group became protocol-mandated Early Escape subjects on Day 113. In the cumulative abatacept period up to Year 1, the mean duration of exposure to abatacept was 10.8 months in subjects who received abatacept during the short term and open label periods and 6.5 months in subjects who received placebo during the short term period and then open label abatacept (either at Day 113 (early escape subjects] or at Day 169). The mean numbers of injections in the abatacept group (20.1 (range: 1 to 26)) and in the placebo group (18.6 (range: 3 to 24)) were consistent with the study design for the short term period. During the open label and long term extension phase, the mean duration of exposure to abatacept was 12.5 months (range: 2 to 25 months) for the reporting period up to 2 years and > 20% of subjects continued to be treated with abatacept for more than 18 months. The overall abatacept exposure for subjects was 408.6 patient-years (p-y). The mean number of abatacept injections administered to all subjects was 45.6 injections (range: 1 to 101). A total of 32% of all subjects had at least 60 injections. Overall, about 170 subjects received abatacept SC 125 mg weekly for >12 months in the cumulative period up to year 2 (see Table 8).

Table 8: Extent of exposure in Study IM101332

Extent of Exposure (Days) to Study Drug during the Short-term Period - IM101332 - As-treated Population

Days of Exposure	Number (%) of Subjects: Abatacept SC N=213	Placebo N=211
<= 84	3 (1.4)	3 (1.4)
> 84 - 141	78 (36.6)	106 (50.2)
> 141 - 169	98 (46.0)	76 (36.0)
> 169	34 (16.0)[a]	26 (12.3)[a]
Mean Days of Exposure (SD)	147.7 (30.5)	140.3 (30.0)
Median (Range)	168.0 (57-218)	134.0 (71-214)

[a] Many subjects entered the dose for the Month 6 visit on the OL case report form. As a result, the first dose of OL was recorded as being taken after the Month 6 visit.

Interruptions in therapy were not deducted from calculation of days of exposure.
For subjects who discontinue during the short-term period or subjects who enter the open-label period after 56 days post the last dose of the short-term period, Days of Exposure = (date of last dose in the short-term - date of first dose in the short-term) + 1 + 56.
For subjects who enter the open-label period within 56 days of the last dose of the short-term period, Days of Exposure = date of first dose in the open-label period - date of first dose in short-term.

Extent of Exposure (Months) to Subcutaneous Abatacept During the Cumulative Abatacept Period Up to Year 1: Cumulative Abatacept Population

Months of Exposure	Number (%) of Subjects: Abatacept SC N=213	Placebo N=185	Total N=398
<= 3	3 (1.4)	0	3 (0.8)
> 3 - 6	8 (3.8)	12 (6.5)	20 (5.0)
> 6 - 9	18 (8.5)	173 (93.5)[a]	191 (48.0)
> 9 - 12	75 (35.2)	0	75 (18.8)
> 12	109 (51.2)	0	109 (27.4)
Mean Months of Exposure (SD)	10.8 (2.3)	6.5 (0.7)	8.8 (2.8)
Median (Range)	12.1 (2-14)	6.5 (3-8)	7.3 (2-14)

[a] Many subjects entered the dose for the Month 6 visit on the OL case report form. As a result, the first dose of OL was recorded as being taken after the Month 6 visit.

In Study IM101158, the mean duration of exposure to abatacept IV (monthly) in the short term period ranged from 153.6 to 166.8 days; the median duration of exposure to study drug in the short term period was 168 days for each of the four treatment groups, consistent with the planned 6 month duration of this period. The median number of infusions of study drug in each treatment group (7.0) was also consistent with the protocol-specified number for the short term period. During the cumulative short term and long term period, the overall mean duration of exposure to abatacept was 20.4 months with over 100 patients receiving abatacept IV over the cumulative short term and open label long term periods of the study (see Table 9).

Overall exposure to abatacept SC (125mg weekly) was adequate to evaluate short-term and long-term safety in the Phase III Study IM101332 (Table 8). However, < 40 patients received treatment with proposed abatacept 10 mg/kg IV during the short term, 6 month controlled period, of the Phase IIb study although overall >150 patients were exposed to IV abatacept over the cumulative short term and open label, long term periods of the study (see Table 9).

Table 9: Extent of exposure in the Phase IIb Study IM101158

Extent of Exposure (Days) to Study Medication during the Short-term Period, Study IM101158, As-Treated Subjects Population

Days of Exposure	Abatacept 30/10 N=43	Abatacept 10/10 N=40	Abatacept 3/3 N=45	Placebo N=42
	Number (%) of Subjects			
<= 84	2 (4.7)	1 (2.5)	0	3 (7.1)
85 - 169	33 (76.7)[a]	29 (72.5)[a]	34 (75.6)[a]	29 (69.0)[a]
>= 170	8 (18.6)	10 (25.0)	11 (24.4)	10 (23.8)
Mean Days of Exposure (SD)	158.5(25.62)	160.2(22.16)	166.8(12.83)	153.6(34.71)
Median (Range)	168(71.0, 173)	168(71.0, 177)	168(86.0, 182)	168(57.0, 181)

[a] Many subjects entered the dose for the Month 6 visit on the OL case report form. As a result, the first dose of OL was recorded as being taken after the Month 6 visit.

Interruptions in therapy were not deducted from calculation of days of exposure.

Days of Exposure = (date of last dose in the double-blind period - date of first dose in the double-blind period +1) + 56

For subjects who enter the open-label period within 56 days of the last dose of the double-blind period, Days of Exposure = (date of first dose of open-label drug administration - date of first dose during the double-blind period)

Source: Table 6.2.2-1 in IM101158 ST + LT CSR

Extent of Exposure (Months) to Abatacept during the Short-term plus Long-term Periods, Study IM101158 - All Abatacept-treated Subjects

Months of Exposure	All Abatacept (N=161)
	Number (%) of Subjects
1-6	24 (14.9)
7-12	25 (15.5)
13-18	23 (14.3)
19-24	7 (4.3)
25-30	58 (36.0)
31-36	24 (14.9)
Mean Months of Exposure (SD)	20.4(10.74)
Median(Range)	25.0(0.5,34.8)

Months of Exposure=[(date of the last dose - date of the first dose +1 - adjustment +56)]/30. Adjustment is the time span in excess of 56 days: between the last dose in short-term and the first dose in the long-term period.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

During the short term period of Study IM101332, marked elevations in hepatic enzymes were noted in < 1% of subjects in the abatacept group and < 2% of subjects in the placebo group. One subject in the placebo group was reported with a serious adverse event of increased alanine transaminase (ALT) on Day 63 (245 U/L) that was considered related to study drug by the investigator and resulted in treatment discontinuation. During the open label, long term extension phase, markedly abnormal increases ranging from 2.3% to 3.0% of subjects were noted in aspartate aminotransferase (AST), ALT and gamma-glutamyl transpeptidase (GGT).

In Study IM101158, one subject in the abatacept 30/10 mg/kg group had a marked elevation in ALT during the short term period. Markedly elevated ALT and AST values were reported during the long term period for 1 subject each (0.7%). One additional subject had an AE of ALT increased during the long term period. This event was not associated with a marked anomaly, was assessed as mild in severity and unlikely related to study drug.

Renal function and renal toxicity

During the short term period of Study IM101332, marked elevations in kidney function tests were noted in < 2% of subjects in the abatacept group and < 1% of subjects in the placebo group. During the open label, long term extension phase, markedly abnormal increases in blood urea nitrogen (BUN) and creatinine were reported for 3.5% and 4.3% of subjects, respectively.

No subject in Study IM101158 had a marked anomaly in serum creatinine during the short term period. Three subjects (2.1%) had marked elevations in BUN during the long term period; all represented isolated, sporadic occurrences and resolved. None were reported as AEs. Marked elevations in serum creatinine were reported in 4 subjects (2.8%) during the long term period, the marked anomaly resolved for all 4 subjects and none were reported as AEs.

Other clinical chemistry

During the short term period in Study IM101332, the frequencies of blood chemistry parameters that met the sponsor defined marked anomaly criteria was small (typically < 3%) and generally similar in the abatacept and placebo groups (see Table 10).

Levels of all clinical laboratory parameters generally remained stable in both treatment groups during the short term period. Small changes from Baseline (Day 1) to Day 169 in blood chemistry parameters were noted and these changes were similar between the abatacept and placebo groups. During the short term period, the only parameter with markedly abnormal values reported in > 5% of subjects was elevated fasting triglycerides: 5.4% in the placebo group and 3.2% in the abatacept group.

Table 10: Laboratory values meeting the marked abnormality criteria during double blind period; All abatacept treated subjects

	Abatacept 10/10			Abatacept 3/3			Abatacept 30/10		
	N	LOW(%)	HIGH(%)	N	LOW(%)	HIGH(%)	N	LOW(%)	HIGH(%)
Hematology I									
Erythrocyte/Platelet attributes									
Hemoglobin	40	0	NE	45	0	NE	43	0	NE
Hematocrit	40	0	NE	45	0	NE	43	0	NE
Erythrocytes	40	0	NE	45	0	NE	43	0	NE
Platelet Count	40	0	0	45	0	0	43	0	0
Hematology II									
Quantitative WBC									
Leukocytes	40	0	0	45	1(2.2)	1(2.2)	43	0	0
WBC differential count									
Neutrophils + Bands (absolute)	40	0	NE	45	0	NE	43	0	NE
Lymphocytes (absolute)	40	0	0	45	6(13.3)	0	43	2(4.7)	0
Monocytes (absolute)	40	NE	0	45	NE	0	43	NE	0
Basophils (absolute)	40	NE	0	45	NE	0	43	NE	0
Eosinophils (absolute)	40	NE	1(2.5)	45	NE	1(2.2)	43	NE	1(2.3)
Liver and Kidney Function									
Liver function tests									
Alkaline Phosphatase (ALP)	40	NE	0	45	NE	0	43	NE	0
Aspartate Aminotransferase (AST)	40	NE	0	45	NE	0	43	NE	0
Alanine Aminotransferase (ALT)	40	NE	0	45	NE	0	43	NE	1(2.3)
G-Glutamyl Transferase (GGT)	40	NE	0	45	NE	0	43	NE	1(2.3)
Bilirubin, Total	40	NE	0	45	NE	0	43	NE	0
Kidney function tests									
Blood Urea Nitrogen	40	NE	0	45	NE	0	43	NE	0
Creatinine	40	NE	0	45	NE	0	43	NE	0
Electrolytes									
Electrolytes									
Sodium, Serum	40	0	0	45	0	0	43	0	0
Potassium, Serum	40	0	0	45	0	0	43	0	0
Chloride, Serum	40	0	0	45	0	0	43	0	0
Calcium, Total	40	0	0	45	0	0	43	0	0
Phosphorus, Inorganic	40	0	0	45	1(2.2)	0	43	0	0
Other Chemistry Tests									
Glucose tests									
Glucose, Serum	40	2(5.0)	2(5.0)	45	4(8.9)	4(8.9)	43	0	1(2.3)
Glucose, Fasting Serum	12	0	0	12	0	0	16	0	0
Protein tests									
Protein, Total	40	0	0	45	0	0	43	0	0
Albumin	40	0	NE	45	0	NE	43	0	NE
Metabolite tests									
Uric Acid	40	NE	0	45	NE	0	43	NE	0

Table 10a (continued): Laboratory values meeting the marked abnormality criteria during double blind period; Placebo subjects

	Placebo		
	N	LOW(%)	HIGH(%)
Hematology I			
Erythrocyte/Platelet attributes			
Hemoglobin	41	0	NE
Hematocrit	41	0	NE
Erythrocytes	41	0	NE
Platelet Count	41	0	0
Hematology II			
Quantitative WBC			
Leukocytes	41	0	0
WBC differential count			
Neutrophils + Bands (absolute)	41	0	NE
Lymphocytes (absolute)	41	1(2.4)	0
Monocytes (absolute)	41	NE	0
Basophils (absolute)	41	NE	0
Eosinophils (absolute)	41	NE	0
Liver and Kidney Function			
Liver function tests			
Alkaline Phosphatase (ALP)	41	NE	0
Aspartate Aminotransferase (AST)	41	NE	0
Alanine Aminotransferase (ALT)	41	NE	0
G-Glutamyl Transferase (GGT)	41	NE	0
Bilirubin, Total	41	NE	0
Kidney function tests			
Blood Urea Nitrogen	41	NE	0
Creatinine	41	NE	0
Electrolytes			
Electrolytes			
Sodium, Serum	41	0	0
Potassium, Serum	41	1(2.4)	0
Chloride, Serum	41	0	0
Calcium, Total	41	0	0
Phosphorus, Inorganic	41	1(2.4)	0
Other Chemistry Tests			
Glucose tests			
Glucose, Serum	41	0	2(4.9)
Glucose, Fasting Serum	15	0	0
Protein tests			
Protein, Total	41	0	0
Albumin	41	0	NE
Metabolite tests			
Uric Acid	41	NE	0

Includes data up to 56 days post last dose in the double-blind period or start of the open-label period, whichever occurred first.
Source: Annex A, Table S.7.1.

During the long term period, the frequencies of blood chemistry parameters that met the sponsor-defined marked anomaly criteria in the All Treated Subjects in long term period population was small (typically < 3%) (Tables 10 and 10a). Marked abnormalities occurring at > 5% included elevated fasting triglycerides in 5.7% of subjects and elevated serum glucose in 5.3% of subjects. No clinically relevant changes were observed in other clinical chemistry in the short term and open label phase of Study IM101158.

Haematology and haematological toxicity

During the short term period in Study IM101332, the frequencies of haematological parameters that met the sponsor-defined marked anomaly criteria was small (typically < 3%) and generally similar in the abatacept and placebo groups (Tables 10 and 10a). Small changes from Baseline (Day 1) to Day 169 in haematological parameters were noted and these changes were similar between the abatacept and placebo groups. During the long term period, the frequencies of haematological parameters that met the sponsor defined marked anomaly criteria in the All Treated Subjects in long term Period population was small (typically < 3%) (Table 11).

The most frequently occurring marked anomaly in Study IM101158 was markedly low lymphocytes (abatacept 30/10 mg/kg group: 4.7%; abatacept 10/10 mg/kg: 0%; abatacept 3/3 mg/kg: 13.3%; placebo group: 2.4%) (Tables 10 and 10a). Lymphopenia was not reported as an AE in any subject during the short term period. Small changes from baseline (Day 1) to Day 169 in haematologic parameters were noted and these changes were similar between the abatacept and placebo groups.

Table 11: Laboratory values meeting marked abnormality criteria during the long term period; All treated subjects in long term period

	Abatacept		
	N	LOW(%)	HIGH(%)
Hematology I			
Erythrocyte/Platelet attributes			
Hemoglobin	147	0	NE
Hematocrit	147	0	NE
Erythrocytes	147	0	NE
Platelet Count	147	0	0
Hematology II			
Quantitative WBC			
Leukocytes	147	1(0.7)	7(4.8)
WBC differential count			
Neutrophils + Bands (absolute)	147	0	NE
Lymphocytes (absolute)	147	6(4.1)	0
Monocytes (absolute)	147	NE	0
Basophils (absolute)	147	NE	1(0.7)
Eosinophils (absolute)	147	NE	12(8.2)
Liver and Kidney Function			
Liver function tests			
Alkaline Phosphatase (ALP)	145	NE	0
Aspartate Aminotransferase (AST)	143	NE	1(0.7)
Alanine Aminotransferase (ALT)	145	NE	1(0.7)
G-Glutamyl Transferase (GGT)	145	NE	6(4.1)
Bilirubin, Total	145	NE	0
Kidney function tests			
Blood Urea Nitrogen	145	NE	3(2.1)
Creatinine	145	NE	4(2.8)
Electrolytes			
Electrolytes			
Sodium, Serum	145	0	1(0.7)
Potassium, Serum	145	0	0
Chloride, Serum	145	0	0
Calcium, Total	145	0	1(0.7)
Phosphorus, Inorganic	145	0	0
Other Chemistry Tests			
Glucose tests			
Glucose, Serum	144	5(3.5)	11(7.6)
Glucose, Fasting Serum	43	0	2(4.7)
Protein tests			
Protein, Total	145	0	0
Albumin	145	0	NE
Metabolite tests			
Uric Acid	145	NE	0

NE = Not Evaluated
Includes data up to 56 days after the last dose date of the long term period.

Vital signs and clinical examination findings

In Study IM101332 mean and median vital sign parameters remained stable from Day 1 (Baseline) through Day 113 (for early escape subjects and non-early escape subjects) and thereafter to Day 169 (for non-early escape subjects). Mean and median vital sign parameters remained stable from Day 1 of the open label period throughout the cumulative period to Day 449 of the open label period.

Study IM101158 the overall, mean values for all vital sign parameters were within the normal ranges and similar in the three abatacept groups and placebo group throughout the short term period; mean values for all vital sign parameters were within the normal ranges during the long term period.

Immunogenicity and immunological events

In pivotal Study IM101332, the numbers of subjects evaluated for immunogenicity in the abatacept group (203 subjects) and placebo group (198 subjects) were similar in the short term period. During treatment in the short term period, there were 8 subjects (3.9%) in the abatacept group and 17 subjects (8.6%) in the placebo group who tested positive for anti-drug antibodies with respect to Baseline, with the majority of these directed against the IgG portion of the molecule (Table 12). Of the 25 subjects positive for anti-drug antibodies, 7 subjects in the placebo group were early escape subjects. The majority of subjects in the short term period transitioned to open label treatment; hence, few subjects were evaluated for post-treatment immunogenicity after the short term period. In the post-treatment period, CTLA-4-specific antibodies were detected in 3 abatacept-treated subjects and IgG-specific antibodies were detected in 2 placebo treated subjects (Table 12).

Table 12: Proportion of subjects with positive antibody response relative to Baseline (ECL method) during short term period; Immunogenicity population

Study Day	CTLA4 AND POSSIBLY IG n/m (%)	IG AND/OR JUNCTION REGION n/m (%)	Total n/m (%)
Abatacept SC			
Day 85	0/196	3/196 (1.5%)	3/196 (1.5%)
Day 113	0/66	0/66	0/66
Day 169	3/119 (2.5%)	2/119 (1.7%)	5/119 (4.2%)
Overall on Trt	**3/203 (1.5%)**	**5/203 (2.5%)**	**8/203 (3.9%)**
28 days post last dose	1/7 (14.3%)	0/7	1/7 (14.3%)
85 days post last dose	3/5 (60.0%)	0/5	3/5 (60.0%)
168 days post last dose	3/4 (75.0%)	0/4	3/4 (75.0%)
Overall Post Visits	3/8 (37.5%)	0/8	3/8 (37.5%)
Overall	6/206 (2.9%)	5/206 (2.4%)	11/206 (5.3%)
Placebo			
Day 85	3/194 (1.5%)	10/194 (5.2%)	13/194 (6.7%)
Day 113	0/75	5/75 (6.7%)	5/75 (6.7%)
Day 169	0/92	5/92 (5.4%)	5/92 (5.4%)
Overall on Trt	**3/198 (1.5%)**	**14/198 (7.1%)**	**17/198 (8.6%)**
28 days post last dose	0/12	1/12 (8.3%)	1/12 (8.3%)
85 days post last dose	0/9	1/9 (11.1%)	1/9 (11.1%)
168 days post last dose	0/9	1/9 (11.1%)	1/9 (11.1%)
Overall Post Visits	0/17	2/17 (11.8%)	2/17 (11.8%)
Overall	3/201 (1.5%)	16/201 (8.0%)	19/201 (9.5%)

n = Number of subjects who were positive.
m = Number of subjects who were evaluated.

Day 113 sera were collected for subjects who qualified for Early Escape (open-label weekly SC abatacept 125 mg) and were not included in the Day 169 assessment.
At Day 169, all subjects transitioned to open-label

In the cumulative abatacept period, all subjects originally randomised to placebo were transitioned to weekly SC abatacept treatment. In evaluating the anti-drug antibody levels of 17 subjects originally randomised to placebo who tested positive for immunogenicity during the short term Period, 6 subjects tested positive only during the short term period, 6 subjects continued to test positive with similar antibody responses to the IgG portion, 4 subjects had anti-CTLA-4 reactivity (1 on-treatment and 3 off-treatment), and 1 subject discontinued without any follow-up. During the cumulative abatacept period, anti-abatacept antibodies directed at both CTLA-4 and possibly IgG regions, and IgG and/or junction regions were noted at similar frequencies for subjects randomised originally to abatacept or to placebo (Table 13).

During the post-treatment period for the cumulative abatacept population, reactivity against CTLA-4 and possibly IgG regions was detected for all subjects with anti-abatacept reactivity. As expected, a numerically higher proportion of subjects had anti-abatacept antibodies detected during the post-treatment period than during the on-treatment period likely due to the immunomodulatory effect of abatacept on antibody generation. Medical review of AEs in subjects with positive antibody responses directed against abatacept did not identify events suggestive of systemic immune reactions, but this review did identify two events that could be autoimmune in nature (Table 14).

Table 13: Proportion of subjects with positive antibody response relative to Baseline (ECL method) during cumulative abatacept period up to Year 2 (double blind, open label, long term extension period); Immunogenicity population

Treatment Group	Study Day	CTLA4 AND POSSIBLY IG n/m (%)	IG AND/OR JUNCTION REGION n/m (%)	Total n/m (%)
Abatacept SC	Day 85	0/196	3/196 (1.5%)	3/196 (1.5%)
	Day 113	0/66	0/66	0/66
	Day 169	3/119 (2.5%)	2/119 (1.7%)	5/119 (4.2%)
	Day 57 OL	4/175 (2.3%)	3/175 (1.7%)	7/175 (4.0%)
	Day 197 OL	6/117 (5.1%)	2/117 (1.7%)	8/117 (6.8%)
	Overall on Trt	9/206 (4.4%)	10/206 (4.9%)	17/206 (8.3%)
	28 Days Post (ST)	1/7 (14.3%)	0/7	1/7 (14.3%)
	85 Days Post (ST)	3/5 (60.0%)	0/5	3/5 (60.0%)
	168 Days Post (ST)	3/4 (75.0%)	0/4	3/4 (75.0%)
	28 Days Post (OL)	2/20 (10.0%)	0/20	2/20 (10.0%)
	85 Days Post (OL)	3/12 (25.0%)	0/12	3/12 (25.0%)
	168 Days Post (OL)	0/8	0/8	0/8
	28 Days Post (LT)	0/5	0/5	0/5
	85 Days Post (LT)	1/6 (16.7%)	0/6	1/6 (16.7%)
	168 Days Post (LT)	1/3 (33.3%)	0/3	1/3 (33.3%)
	Overall Post Visits	10/36 (27.8%)	0/36	10/36 (27.8%)
	Overall	19/209 (9.1%)	10/209 (4.8%)	26/209 (12.4%)
Placebo	Day 57 OL	0/164	2/164 (1.2%)	2/164 (1.2%)
	Day 197 OL	3/116 (2.6%)	4/116 (3.4%)	7/116 (6.0%)
	Overall on Trt	3/168 (1.8%)	6/168 (3.6%)	9/168 (5.4%)
	28 Days Post (ST)	0/0	0/0	0/0
	85 Days Post (ST)	0/0	0/0	0/0
	168 Days Post (ST)	0/0	0/0	0/0
	28 Days Post (OL)	0/12	0/12	0/12
	85 Days Post (OL)	4/13 (30.8%)	0/13	4/13 (30.8%)
	168 Days Post (OL)	5/10 (50.0%)	0/10	5/10 (50.0%)
	28 Days Post (LT)	1/7 (14.3%)	0/7	1/7 (14.3%)
	85 Days Post (LT)	0/5	0/5	0/5
	168 Days Post (LT)	1/2 (50.0%)	0/2	1/2 (50.0%)
	Overall Post Visits	8/24 (33.3%)	0/24	8/24 (33.3%)
Total	Day 85	0/196	3/196 (1.5%)	3/196 (1.5%)
	Day 113	0/66	0/66	0/66
	Day 169	3/119 (2.5%)	2/119 (1.7%)	5/119 (4.2%)
	Day 57 OL	4/339 (1.2%)	5/339 (1.5%)	9/339 (2.7%)
	Day 197 OL	9/233 (3.9%)	6/233 (2.6%)	15/233 (6.4%)
	Overall on Trt	12/374 (3.2%)	16/374 (4.3%)	26/374 (7.0%)
	28 Days Post (ST)	1/7 (14.3%)	0/7	1/7 (14.3%)
	85 Days Post (ST)	3/5 (60.0%)	0/5	3/5 (60.0%)
	168 Days Post (ST)	3/4 (75.0%)	0/4	3/4 (75.0%)
	28 Days Post (OL)	2/32 (6.3%)	0/32	2/32 (6.3%)
	85 Days Post (OL)	7/25 (28.0%)	0/25	7/25 (28.0%)
	168 Days Post (OL)	5/18 (27.8%)	0/18	5/18 (27.8%)
	28 Days Post (LT)	1/12 (8.3%)	0/12	1/12 (8.3%)
	85 Days Post (LT)	1/11 (9.1%)	0/11	1/11 (9.1%)
	168 Days Post (LT)	2/5 (40.0%)	0/5	2/5 (40.0%)
	Overall Post Visits	18/60 (30.0%)	0/60	18/60 (30.0%)
	Overall	30/378 (7.9%)	16/378 (4.2%)	43/378 (11.4%)

n = Number of subjects who are positive.
m = Number of subjects who are evaluated.
OL = Open-label
Treatment groups represent treatment received in the short-term period.

Table 14: Narratives for the two AEs that may be related to positive antibody response

An SAE of colitis (verbatim term: 'inflammatory colitis') was reported for Subject [information redacted] days post-randomisation, during the open label period, which led to discontinuation. The event was considered unrelated to study drug. The subject was randomised to placebo but received abatacept after Early Escape to open label treatment. At the time of database lock, the event was ongoing. This subject was negative for antibody responses directed against abatacept at Days 1, 85, 113, and at post-study visits on Days 28 and 85. The only antibody response against abatacept detected was on post-study visit Day 168, with a titre of 240. The timing of positive autoantibody response detected on Day 169 after discontinuation does not support a relationship between anti-abatacept antibody positivity and the event of inflammatory colitis.
An AE of moderate hypersensitivity (verbatim term, 'allergic reaction') was reported 530 days post-randomisation, during the long-term extension, for Subject [information redacted]. The subject was originally randomised to abatacept. The event was considered unrelated to study

drug and resulted in no action with respect to study drug. The subject was negative for antibody responses directed against abatacept at Days 1 and 85, but positive at Day 169 of the short term Period and Day 197 of the open label period (360 days post-randomisation; reactivity against CTLA-4). No subsequent immunogenicity testing was available. Because the subject continued in the study and tolerated subsequent dosing without incident, this event of hypersensitivity was unlikely to be related to abatacept or anti-abatacept antibodies. The subject also had the following AEs: oedema peripheral (Day 140), vitamin D deficiency (Day 191), nasopharyngitis (Day 202), nasopharyngitis (Day 361), cough (Day 361), abdominal pain (Day 363), pyrexia (Day 438), gastric mucosa erythema (Day 444 and 457), hyperparathyroidism (Day 458) and nasopharyngitis (Day 514).

In Study IM101158, total of 1 (2.3%), 0 and 2 (4.4%) subjects in the abatacept 30/10 mg/kg, abatacept 10/10 mg/kg, and abatacept 3/3 mg/kg groups, respectively, demonstrated positive immunogenicity reactivity. Of the 3 subjects with anti-abatacept antibodies, 2 subjects demonstrated anti-abatacept antibodies only at Day 169. None of the subjects with anti-abatacept antibodies were reported to have SAEs, acute infusional AEs (prespecified), or autoimmune disorders (prespecified).

The overall abatacept-induced immunogenicity rate for the long term period, based on the ECL assay, was 8.2% (12 out of 147) (Table 15) with the on-treatment immunogenicity rate of 3.4% (5 out of 145) and the post-treatment immunogenicity rate of 7.1% (9 out of 126). All of the abatacept-induced seropositive responses in the long term period consisted of 'CTLA-4 and possibly Ig' (none for 'Ig and/or Junction Region'). Medical review of the safety data among subjects with an abatacept-induced seropositive response in the long term period indicated that AEs were not consistent with immune-mediated toxicities, and no subject with an abatacept-induced seropositive result had a SAE. One subject with an abatacept-induced seropositive response had an autoimmune disorder (psoriasis exacerbation) that had an onset approximately 3 months after the occurrence of seropositive finding.

Table 15: Proportion of subjects with positive abatacept induced responses (ECL method) over time in the long term period. Immunogenicity population of long term period

Treatment Group	Study Day	CTLA4 AND POSSIBLY IG n/m (%)	IG AND/OR JUNCTION REGION n/m (%)	Total n/m (%)
Abatacept 30/10	On treatment	2/ 37 (5.4%)	0/ 37	2/ 37 (5.4%)
	Post treatment	1/ 32 (3.1%)	0/ 32	1/ 32 (3.1%)
	Overall	2/ 37 (5.4%)	0/ 37	2/ 37 (5.4%)
Abatacept 10/10	On treatment	2/ 34 (5.9%)	0/ 34	2/ 34 (5.9%)
	Post treatment	2/ 25 (8.0%)	0/ 25	2/ 25 (8.0%)
	Overall	3/ 34 (8.8%)	0/ 34	3/ 34 (8.8%)
Abatacept 3/3	On treatment	0/ 42	0/ 42	0/ 42
	Post treatment	2/ 37 (5.4%)	0/ 37	2/ 37 (5.4%)
	Overall	2/ 43 (4.7%)	0/ 43	2/ 43 (4.7%)
Placebo	On treatment	1/ 32 (3.1%)	0/ 32	1/ 32 (3.1%)
	Post treatment	4/ 32 (12.5%)	0/ 32	4/ 32 (12.5%)
	Overall	5/ 33 (15.2%)	0/ 33	5/ 33 (15.2%)
Total	On treatment	5/ 145 (3.4%)	0/ 145	5/ 145 (3.4%)
	Post treatment	9/ 126 (7.1%)	0/ 126	9/ 126 (7.1%)
	Overall	12/ 147 (8.2%)	0/ 147	12/ 147 (8.2%)

n = Number of subjects who are positive.
m = Number of subjects who are evaluated.
On treatment includes data upto 42 days after the date of the last dose of long term period.

Serious skin reactions

No serious skin reactions were reported in Study IM101332 or Study IM101158.

AEs of special interest (AESIs) Study IM101332

In Study IM101332, adverse events of special interest (infections, malignancies, autoimmune events, local injection site reactions, and AEs occurring within 24 hours of

drug administration) were reported in similar proportions of subjects in each treatment group during the short term period (Table 16).

Table 16: AEs of special interest reported during the short-term period; As treated population

	n (%) Abatacept SC (N=213)	Placebo (N=211)
TOTAL SUBJECTS WITH INFECTIONS AND INFESTATIONS	57 (26.8)	63 (29.9)
TOTAL SUBJECTS WITH MALIGNANCIES	0	2 (0.9)
TOTAL SUBJECTS WITH AUTOIMMUNE EVENTS	0	0
TOTAL SUBJECTS WITH LOCAL INJECTION SITE REACTIONS	1 (0.5)	1 (0.5)
TOTAL SUBJECTS WITH AE WITHIN 24 HR	39 (18.3)	39 (18.5)

Includes data up to 56 days post the last dose in the ST Period or the first dose in the Open-label Period, whichever occurred first.
MEDDRA VERSION: 18.0

AEs of special interest during the open label, long term extension phase are summarised in Table 17.

Table 17: Incidence rates of AEs of special interest during cumulative abatacept period up to Year 2 (double blind, open label, long term extension period); Cumulative abatacept population (Year 2)

TREATMENT GROUP: Abatacept SC (N=398)

	ABATACEPT SC EXPOSURE			
	SUBJECTS WITH EVENT (%)	EXPOSURE (PERSON-YEARS)	RATE: (INCIDENCE/100 PERSON-YEARS)	POISSON 95% CI
TOTAL SUBJECTS WITH INFECTIONS AND INFESTATIONS[a]	181 (45.5)	270.79	66.84	(57.76, 77.32)
TOTAL SUBJECTS WITH Malignancies	3 (0.8)	408.13	0.74	(0.24, 2.28)
TOTAL SUBJECTS WITH Autoimmune Events (Pre-specified)	2 (0.5)	409.29	0.49	(0.12, 1.95)
TOTAL SUBJECTS WITH Local Injection Site Reactions (Pre-specified)	5 (1.3)	405.79	1.23	(0.51, 2.96)
TOTAL SUBJECTS WITH Adverse Events within 24-hr.	102 (25.6)	323.61	31.52	(25.96, 38.27)

[a] System Organ Class for infections
Includes data from the first day of the double blind period for subjects randomized and treated with abatacept and from the first day of Open-label Period for subjects randomized and treated with placebo up to 56 days post the last abatacept dose in the study.
Rate: (incidence/100 person-years) = number of subjects with event * 100 /exposure (person-years)
Exposure (person-years) = the sum over all subjects of the Abatacept exposure per subject in cumulative abatacept period up to Year 2 (censored at the time of first occurrence of AE) expressed in days, divided by 365.25.
For subjects who discontinue in the short-term, Open-label or long-term extension includes data up to 56 days post last abatacept dose in the study.
MEDDRA VERSION: 18.0

Infections

Short term period: The most frequently reported AEs of infection in the abatacept and placebo groups were nasopharyngitis (4.2% and 5.2% of subjects, respectively) and upper respiratory tract infections (2.8% and 6.6% of subjects). AEs reported in at least 2% of subjects and in more subjects in the abatacept versus placebo groups included urinary tract infections (4.2% versus 0.9% of subjects), bronchitis (3.3% versus 2.4% of subjects) and gastroenteritis (3.3% versus 2.4% of subjects). AEs in the System Organ classification (SOC) of Infections and Infestations considered related to study drug were reported in both treatment groups at similar frequencies; the most frequently reported AEs considered related to study drug in the abatacept and placebo groups were bronchitis (0.9% versus 0.9%), influenza (0.9% versus 0.5%) and upper respiratory tract infections (0.5% versus 0.9%). Infections leading to discontinuation of study drug treatment were reported in 1.4% of subjects in the abatacept group and in 0% subjects in the placebo group (Table 18). Serious infections were reported in 1.4% of subjects in the abatacept group and 0.9% of subjects in the placebo group.

Table 18: Study IM101332 Summary of safety results during the short-term period; As treated population

	Number (%) of Subjects	
	Abatacept (N=213)	Placebo (N=211)
Deaths	0	0
SAEs	6 (2.8)	9 (4.3)
Related SAEs	1 (0.5)	1 (0.5)
Discontinued due to SAEs	3 (1.4)	3 (1.4)
Discontinued due to AEs	3 (1.4)	4 (1.9)
AEs	116 (54.5)	112 (53.1)
Related AEs	33 (15.5)	24 (11.4)
AEs Reported in ≥ 5% of Subjects		
Nasopharyngitis	9 (4.2)	11 (5.2)
Upper Respiratory Tract Infection	6 (2.8)	14 (6.6)
AEs of Special Interest		
Infections[a]	57 (26.8)	63 (29.9)
Malignancies	0	2 (0.9)
Autoimmune Events	0	0
Local Injection Site Reactions	1 (0.5)	1 (0.5)
AEs within 24 hr	39 (18.3)	39 (18.5)
Marked Laboratory Abnormalities in ≥ 5% of Subjects		
Elevated Triglycerides, Fasting	5 (3.2)	8 (5.4)

[a] SOC of Infections and Infestations
Includes data up to 56 days post the last dose in the ST Period or the first dose in the Open-label Period, whichever occurred first.
MEDDRA VERSION: 18.0

Open label, long term extension phase*:* Infections and Infestations were the predominant AEs reported (incidence rate: 66.8 per 100 p-y). Upper respiratory infections (incidence rate: 8.6 per 100 p-y), bronchitis (incidence rate: 8.1 per 100 p-y), nasopharyngitis (incidence rate: 6.6 per 100 p-y) and urinary tract infections (incidence rate: 5.6 per 100 p-y) were the only AEs reported in > 5% of subjects. Infections leading to treatment discontinuation occurred in 5 subjects (1.3%). Serious infections were reported in 8 subjects (2.0%) and the incidence rate for SAEs of infection was 1.97 per 100 p-y.

Malignancies

Short term period: No malignancies were reported in the abatacept group. Two (2) malignancies were reported in the placebo group; B-cell lymphoma and invasive ductal breast carcinoma were SAEs unrelated to study drug that resulted in treatment discontinuation.

Open label, long term extension phase: *Three (3) malignancies (incidence rate: 0.74 per 100 p-y) in 3 subjects originally randomised to placebo were reported during open label treatment with abatacept: carcinoma in situ of the skin (a serious adverse event, mild in intensity, no discontinuation, resolved, medical history of benign skin tumour), prostate cancer (a serious adverse event, severe in intensity, resulting in discontinuation, ongoing, medical history of benign prostatic hypertrophy) and squamous cell carcinoma of the skin (nose) (not an SAE, moderate in intensity, no discontinuation, resolved, medical history of basalioma of the nose).*

Autoimmune events

Short term period: No autoimmune events (pre-specified) were reported in either treatment group. However, it is important to note that investigators were requested to not report AEs of psoriatic arthritis or psoriasis unless the event represented a new form of psoriasis or was an SAE.

Open label, long term extension phase: Pre-specified autoimmune events (incidence rate: 0.49 per 100 p-y) were reported in 2 out of 398 subjects, both of whom originally randomised to receive abatacept. Uveitis was reported in 1 subject during the open label period and coeliac disease in another subject during the long term extension. Neither AE was considered related to abatacept nor was treatment discontinued for either subject due to the AE.

Local injection site reactions

Short term period: One (1) subject in each treatment group had a pre-specified local injection site reaction. Two (2) AEs of mild injection site pruritus were reported in 1 subject in the abatacept group considered to be related to study drug and mild injection site oedema was reported in 1 subject in the placebo group considered not related to study drug. No subject discontinued therapy due to these AEs.

Open label, Long term extension phase*:* Pre-specified local injection site reactions (incidence rate: 1.23 per 100 p-y), all mild in intensity, were reported in 5 out of 398 subjects: 1 subject with an injection site reaction (related to abatacept), 1 subject with two episodes of puncture site erythema (both episodes not related to abatacept), 1 subject with three episodes of injection site erythema (all episodes related to abatacept), and 1 subject with injection site erythema (related to abatacept). A fifth subject in the original abatacept treatment group was reported with two episodes of pruritus (related to abatacept). No subject discontinued therapy due to these AEs.

AEs occurring within 24 hr of drug administration

Short term period*:* A similar proportion of subjects in the abatacept and placebo groups (39 subjects in each group: 18.3% and 18.5%, respectively) had one or more AEs within 24 hr of study drug administration; none of the events were suggestive of systemic drug reactions. The incidence rates per 100 p-y for AEs overall within 24 hr were 53.4 for the abatacept group and 71.6 for the placebo group. The most frequently reported AEs within 24 hr were in the SOC of Infections and infestations: 13 subjects (6.1%, incidence rate: 15.1 per 100 p-y) in the abatacept group and 15 subjects (6.2%; incidence rate: 18.5 per 100 p-y) in the placebo group. Within this SOC, the most frequently reported individual AEs were urinary tract infection (3 subjects [1.4%], abatacept group; 1 subject [0.5%], placebo group), followed by oral herpes (2 subjects [0.9%], abatacept group; 1 subject [0.5%], placebo group) and upper respiratory tract infection (1 subject [0.5%], abatacept group; 2 subject [0.9%], placebo group). Based on clinical review, there were no AEs within 24 hr of study drug administration suggestive of systemic medication reaction.

Open label, *l*ong term extension phase: Overall, 102 subjects (25.6%) were reported with an AE within 24 hr of drug administration, corresponding to an incidence rate of 31.52 per 100 p-y. None of these events were suggestive of systemic drug reactions. Incidence rates

were highest for Infections and Infestations (incidence rate: 10.66 per 100 p-y), with the AE of nasopharyngitis having the highest individual incidence rate (that is, 1.48 per 100 p-y).

AEs of new psoriasis or SAEs of psoriasis or psoriatic arthropathy

Investigators were requested not to report any psoriasis or any psoriatic arthritis as AEs unless they were new forms of psoriasis or SAEs of psoriasis or psoriatic arthritis.

Short term period: The following AEs (considered by the investigator to be unrelated to study drug) were reported in 4 subjects in the placebo group: nail psoriasis (new), psoriasis (new inverse psoriasis), and 2 subjects with psoriatic arthropathy (worsening/exacerbation). For 1 of the 2 subjects with psoriatic arthropathy, the event was reported as an SAE; this SAE occurred again in this subject during the open label period when the subject was receiving abatacept. None of these AEs/serious AEs led to discontinuation of study therapy; however, the subject with a serious adverse event (SAE) of psoriatic arthropathy (worsening) transitioned to the Early Escape group and received open label abatacept.

Open label, *l*ong term extension phase*:* The following AEs (considered not related to abatacept) were reported in 3 subjects, all originally randomised to placebo treatment: psoriasis (flare, an SAE in 1 subject), psoriasis (worsening, an AE in 1 subject) and psoriatic arthropathy (worsening, 2 SAEs in 1 subject in short term period and open label period). None of these AEs resulted in discontinuation of treatment In addition, 1 subject originally randomised to abatacept treatment was reported with an AE and also an SAE of erythrodermic psoriasis during the open label period; both AE and SAE were considered related to abatacept by the investigator. This subject discontinued treatment due to lack of efficacy.

AEs of special interest (AESI) in Study IM101158

Infections

A similar percentage of subjects in each treatment group in Study IM101158 had an AE in the SOC, Infections and Infestations, up to 56 days after the last infusion in the short term period or the start of the long term period, whichever occurred first: 34.9%, 35.0%, 35.6% and 35.7% in the abatacept 30/10 mg/kg, abatacept 10/10 mg/kg, abatacept 3/3 mg/kg, and placebo groups, respectively (Table 19).

Table 19: Infections and Infestations AEs reported during the double blind period; All treated subjects

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept 30/10 N = 43	Abatacept 10/10 N = 40	Abatacept 3/3 N = 45	Placebo N = 42
INFECTIONS AND INFESTATIONS	15 (34.9)	14 (35.0)	16 (35.6)	15 (35.7)
NASOPHARYNGITIS	4 (9.3)	4 (10.0)	5 (11.1)	4 (9.5)
UPPER RESPIRATORY TRACT INFECTION	2 (4.7)	1 (2.5)	3 (6.7)	2 (4.8)
INFLUENZA	0	1 (2.5)	2 (4.4)	2 (4.8)
SINUSITIS	2 (4.7)	2 (5.0)	1 (2.2)	2 (4.8)
CYSTITIS	0	0	0	2 (4.8)
GASTROENTERITIS VIRAL	0	0	1 (2.2)	1 (2.4)
BRONCHITIS	3 (7.0)	1 (2.5)	0	1 (2.4)
RESPIRATORY TRACT INFECTION	1 (2.3)	1 (2.5)	0	1 (2.4)
GASTROENTERITIS	0	1 (2.5)	0	1 (2.4)
EAR INFECTION	1 (2.3)	0	0	1 (2.4)
ACNE DERMATITIS	0	0	0	1 (2.4)
PHARYNGITIS STREPTOCOCCAL	0	0	0	1 (2.4)
URINARY TRACT INFECTION	0	0	2 (4.4)	0
PYELONEPHRITIS	0	2 (5.0)	1 (2.2)	0
GINGIVAL INFECTION	0	0	1 (2.2)	0
LOCALISED INFECTION	0	0	1 (2.2)	0
ORAL HERPES	0	0	1 (2.2)	0
PERIODONTAL INFECTION	0	0	1 (2.2)	0
TOOTH INFECTION	0	2 (5.0)	0	0
FOLLICULITIS	0	1 (2.5)	0	0
HERPES ZOSTER	0	1 (2.5)	0	0
LOWER RESPIRATORY TRACT INFECTION	0	1 (2.5)	0	0
VIRAL MENINGITIS	0	1 (2.5)	0	0
OTITIS MEDIA	2 (4.7)	0	0	0
BODY TINEA	1 (2.3)	0	0	0
EXTERNAL EAR CELLULITIS	1 (2.3)	0	0	0
OSTEOMYELITIS	1 (2.3)	0	0	0
TINEA PEDIS	1 (2.3)	0	0	0

Includes data up to 56 days post the last dose in the double-blind period or start of the open-label period, whichever occurred first.

These reported events include bacterial, viral and fungal infections. Nasopharyngitis was the most frequently reported infection in all 4 treatment groups, reported for 9.3% to 11.1% of subjects in the abatacept treatment groups and for 9.5% of subjects in the placebo group. All reported infection and infestation AEs during the short term period were mild or moderate in severity, except for 1 event in the abatacept 30/10 mg/kg group (osteomyelitis, very severe. Infection or infestation AEs assessed by the investigator as related to study drug were also reported at similar rates during the short term period in the abatacept 30/10 mg/kg (14.0%), 10/10 mg/kg (10.0%), 3/3 mg/kg (13.3%) and placebo (9.5%) groups. During the short term period, infection or infestation AEs were serious in 2 abatacept treated subjects, and no placebo treated subject.

During the long term period, AEs in the SOC, Infections and Infestations, were reported in 83 subjects (56.5%) in the All Treated Subjects in long term Period population (Table 20).

The most commonly reported infection AEs during the long term period were nasopharyngitis (22.4%), upper respiratory tract infection (10.9%), bronchitis (8.8%), sinusitis (8.2%) and urinary tract infection (6.8%). One of the reported AEs in this SOC (tooth abscess) was assessed as severe in intensity. For 5 subjects (3.4%), the reported infection in the long term period was serious (including 2 reports of pneumonia). For 3 of these subjects, the SAEs were assessed as at least possibly related to study treatment (cellulitis, herpes zoster, pyelonephritis acute and pneumonia). For the All Abatacept-treated Subjects population, a total of 100 subjects (62.1%) of subjects had at least 1 AE in the SOC, Infections and Infestations, across the short term and/or long term periods).

Nasopharyngitis (25.5%), upper respiratory tract infection (11.8%), sinusitis (9.9%), bronchitis (9.3%) and urinary tract infection (6.2%) were the most common infectious AEs reported in subjects exposed to abatacept in this study. For only 2 abatacept-treated subjects, were the infectious AEs assessed as severe (tooth abscess) or very severe (osteomyelitis) in intensity.

Table 20: Infections and infestations AEs reported during the long term period; All treated subjects in long term period Includes data up to 56 days post the last dose in the long term period

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 147
TOTAL SUBJECTS WITH AEs	123 (83.7)
INFECTIONS AND INFESTATIONS	83 (56.5)
NASOPHARYNGITIS	33 (22.4)
UPPER RESPIRATORY TRACT INFECTION	16 (10.9)
BRONCHITIS	13 (8.8)
SINUSITIS	12 (8.2)
URINARY TRACT INFECTION	10 (6.8)
ORAL HERPES	5 (3.4)
GASTROENTERITIS	4 (2.7)
INFLUENZA	4 (2.7)
FUNGAL SKIN INFECTION	3 (2.0)
HERPES ZOSTER	3 (2.0)
LOWER RESPIRATORY TRACT INFECTION	3 (2.0)
PNEUMONIA	3 (2.0)
TOOTH ABSCESS	3 (2.0)
CELLULITIS	2 (1.4)
CYSTITIS	2 (1.4)
FOLLICULITIS	2 (1.4)
HERPES SIMPLEX	2 (1.4)
LOCALISED INFECTION	2 (1.4)
ORAL CANDIDIASIS	2 (1.4)
PHARYNGITIS	2 (1.4)
TINEA PEDIS	2 (1.4)
TOOTH INFECTION	2 (1.4)
VAGINAL INFECTION	2 (1.4)
VIRAL UPPER RESPIRATORY TRACT INFECTION	2 (1.4)
VULVOVAGINAL MYCOTIC INFECTION	2 (1.4)
CHRONIC SINUSITIS	1 (0.7)
DACRYOCANALICULITIS	1 (0.7)
DIVERTICULITIS	1 (0.7)
EAR INFECTION	1 (0.7)
ENTEROCOLITIS VIRAL	1 (0.7)
INFECTIONS AND INFESTATIONS (cont'd)	
GASTROINTESTINAL INFECTION	1 (0.7)
GENITAL INFECTION FUNGAL	1 (0.7)
HERPES DERMATITIS	1 (0.7)
KIDNEY INFECTION	1 (0.7)
LOBAR PNEUMONIA	1 (0.7)
OTITIS EXTERNA	1 (0.7)
OTITIS MEDIA	1 (0.7)
PEPTOSTREPTOCOCCUS INFECTION	1 (0.7)
PYELONEPHRITIS ACUTE	1 (0.7)
RESPIRATORY TRACT INFECTION	1 (0.7)
RHINITIS	1 (0.7)
SIALOADENITIS	1 (0.7)
SKIN CANDIDA	1 (0.7)
SUBCUTANEOUS ABSCESS	1 (0.7)
TINEA CRURIS	1 (0.7)

Malignancies

A single malignancy was reported during the short term period: basal cell carcinoma in a subject in the abatacept 30/10 mg/kg group.

Malignancies were reported in 2 subjects (1.4%) treated with abatacept during the long term period. Both of these malignancies (Bowen's disease, lentigo maligna stage unspecified) were assessed as moderate in intensity and unlikely or not related to study drug. Neither of the malignancies resulted in discontinuation and both resolved. A third subject was diagnosed with metastatic squamous cell carcinoma of the tongue; this AE was reported (Day 761) approximately 90 days after the last dose of abatacept in the long term period (Day 673).

Autoimmune disorders

Autoimmune disorder AEs (prespecified) were reported during the short term period for 4 subjects, including 3 subjects (7.5%) in the abatacept 10/10 mg/kg group (mild psoriasis, severe psoriasis and moderate psoriatic arthropathy) and 1 subject (2.4%) in the placebo group. These autoimmune disorders of psoriasis and psoriatic arthropathy were part of the underlying disease under study and were unlikely or unrelated to the study drug.

Autoimmune disorders (prespecified) were reported for 5 (3.4%) treated subjects during the long term period. For each of these subjects, the autoimmune disorder (psoriasis) was not new, but was part of the underlying disease under study and were assessed as unlikely or not related to study treatment.

Infusional AEs

Acute infusional AEs (prespecified), occurring within 1 hr of infusion, were reported during the short term period in a total of 4 abatacept-treated subjects, including 2 (4.7%) in the abatacept 30/10 mg/kg group and 2 (5.0%) in the abatacept 10/10 mg/kg group. No subject in the abatacept 3/3 mg/kg or placebo groups had an acute infusional AE during the short term period. None of the reported acute infusional AEs (prespecified) during the short term period were serious and all were of mild to moderate severity, except for one. During the short term period, peri-infusional AE (prespecified) (occurring within 24 hr after the start of study drug infusion) were reported in 4 subjects (9.3%) in the abatacept 30/10 mg/kg group, 6 subjects (15.0%) in the abatacept 10/10 mg/kg group, 3 subjects (6.7%) in the abatacept 3/3 mg/kg group, and 3 subjects (7.1%) in the placebo group (Table 21). Most of these AEs (PTs) were reported by only a single subject across all 4 treatment groups; those that were reported by more than 1 abatacept-treated subject were headache (n = 3), infusion related reaction (n = 2), blood pressure increased (n = 2) and dizziness (n = 2). None of the reported peri-infusional AEs (prespecified) during the short term period were serious. All were of mild to moderate severity, except for the severe anaphylactic reaction that was reported within 1 hr of start of study infusion. Two peri-infusional AEs reported during the short term period resulted in discontinuation: anaphylactic reaction in abatacept 10/10 mg/kg group (acute infusional AE discussed above) and infusion related reaction also in the abatacept 10/10 mg/kg group.

Table 21: Peri-infusional AEs (prespecified) reported during double blind period; All treated subjects

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept 30/10 N = 43	Abatacept 10/10 N = 40	Abatacept 3/3 N = 45	Placebo N = 42
TOTAL SUBJECTS WITH PERI-INFUSIONAL AE	4 (9.3)	6 (15.0)	3 (6.7)	3 (7.1)
CARDIAC DISORDERS	0	1 (2.5)	0	0
BRADYCARDIA	0	1 (2.5)	0	0
GASTROINTESTINAL DISORDERS	0	1 (2.5)	0	1 (2.4)
NAUSEA	0	0	0	1 (2.4)
VOMITING	0	1 (2.5)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	3 (7.5)	0	0
INFUSION RELATED REACTION	0	2 (5.0)	0	0
ASTHENIA	0	1 (2.5)	0	0
IMMUNE SYSTEM DISORDERS	0	2 (5.0)	0	0
ANAPHYLACTIC REACTION	0	1 (2.5)	0	0
HYPERSENSITIVITY	0	1 (2.5)	0	0
INVESTIGATIONS	2 (4.7)	0	0	0
BLOOD PRESSURE INCREASED	2 (4.7)	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	1 (2.2)	0
ARTHRALGIA	0	0	1 (2.2)	0
NERVOUS SYSTEM DISORDERS	2 (4.7)	1 (2.5)	2 (4.4)	3 (7.1)
HEADACHE	1 (2.3)	0	2 (4.4)	2 (4.8)
DIZZINESS	1 (2.3)	1 (2.5)	0	1 (2.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (2.3)	0	0	0
DYSPNOEA	1 (2.3)	0	0	0
VASCULAR DISORDERS	1 (2.3)	0	0	0
FLUSHING	1 (2.3)	0	0	0

Includes data up to 56 days post the last dose in the double-blind period or start of the open-label period, whichever occurred first.

All peri-infusional AEs except for 1 (bradycardia in abatacept 10/10 mg/kg group) resolved, most within 1 day.

Acute infusional AEs reported within 1 hr after the start of study drug infusion were reported by 4 (2.7%) treated subjects during the long term period. These events included 2 reports of infusion related reaction, and single reports each of pruritus and flushing. None of the acute infusional AEs were serious or resulted in discontinuation of abatacept. All were mild or moderate in intensity, and resolved within 24 hr. Peri-infusional AEs, reported within 24 hr after the start of study drug infusion, were reported by 11 (7.5%) subjects during the long term period. Headache (n = 3, 2.0%) and infusion related reaction

(n = 2, 1.4%) were the individual peri-infusional AEs reported in more than 1 subject. No serious peri-infusional AEs were reported during the long term period. All reported peri-infusional AEs during the long term period were mild or moderate in intensity except for one report of headache (severe). None of the peri-infusional AEs in the long term period resulted in discontinuation of study drug and all resolved.

Safety in special populations

Subgroup analyses for safety were performed in the pivotal Phase III Study IM101332 only. Based upon the prespecified criterion that only subgroups consisting of 10% or more of the population would be considered, AEs were analysed for the following subgroups: age (< 65 years old, > 65 years old), baseline weight 60 to 100 kg, > 100 kg), gender (male, female), geographic region (North America, Europe, South America, ROW), MTX use at Day 1 (yes, no) and TNFi-exposed (yes, no). No clinically relevant differences were observed between treatment groups for any subgroup.

Intrinsic factors: Age, baseline weight, gender

Short term period: Proportions of subjects < 65 years of age with AEs were comparable to subjects > 65 years of age, although some AEs were numerically higher in the older cohort. A total of 10.1% of subjects were > 65 years of age. There were no clinically relevant differences in AEs between the treatment groups for subjects in the two age groups. Although incidence of AEs was slightly higher in the abatacept group compared to placebo in the subgroup > 65 years while incidence was similar in the subgroup < 65 years, interpretation was limited by small number of patients in the > 65 years subgroup (Table 22).

Table 22: AEs reported during the short-term period by age; As treated population

	Number of Subjects (%)[a]			
	Age < 65 years old		Age ≥ 65 years old	
Preferred Term	Abatacept SC N=191	Placebo N=190	Abatacept SC N=22	Placebo N=21
Total Subjects with AEs	**101 (52.9)**	**100 (52.6)**	**15 (68.2)**	**12 (57.1)**
Upper Respiratory Tract Infection	6 (3.1)	13 (6.8)	0	1 (4.8)
Nasopharyngitis	7 (3.7)	10 (5.3)	2 (9.1)	1 (4.8)
Bronchitis	5 (2.6)	5 (2.6)	2 (9.1)	0
Gastroenteritis	7 (3.7)	3 (1.6)	0	2 (9.5)
Urinary Tract Infection	8 (4.2)	2 (1.1)	1 (4.5)	0
Influenza	4 (2.1)	3 (1.6)	0	0
Sinusitis	4 (2.1)	3 (1.6)	0	0
Diarrhea	2 (1.0)	2 (1.1)	0	2 (9.5)
Nausea	2 (1.0)	4 (2.1)	1 (4.5)	1 (4.8)
Back Pain	4 (2.1)	2 (1.1)	0	0
Pyrexia	4 (2.1)	3 (1.6)	0	0
Oedema Peripheral	6 (3.1)	0	0	0
Cough	4 (2.1)	3 (1.6)	1 (4.5)	0
Dyslipidaemia	4 (2.1)	0	0	0
Headache	2 (1.0)	3 (1.6)	2 (9.1)	1 (4.8)
Hypertension	4 (2.1)	6 (3.2)	1 (4.5)	1 (4.8)
Fatigue	2 (1.0)	2 (1.1)	2 (9.1)	0

[a]AEs reported in ≥2% of subjects under 65 years, and ≥2 subjects ≥65 years (due to small subgroup size).

Includes data up to 56 days post the last dose in the ST Period or the first dose in the Open-label Period, whichever occurred first. MEDDRA VERSION: 18.0

Overall, the proportions of subjects with AEs with baseline weights of 60 to 100 kg were generally similar to those subjects weighing > 100 kg. Individual AEs were reported by

comparable proportions of subjects in the two weight groups with no clinically relevant differences in AEs between the treatment groups for subjects in the two weight groups (Table 23).

Table 23: AEs reported during the short term period by Baseline weight; As treated population

	Number of Subjects (%)[a]			
	Weight 60-100 kg		Weight ≥ 100 kg	
Preferred Term	Abatacept SC N=158	Placebo N=152	Abatacept SC N=39	Placebo N=44
Total Subjects with AEs	**88 (55.7)**	**81 (53.3)**	**22 (56.4)**	**25 (56.8)**
Upper Respiratory Tract Infection	3 (1.9)	9 (5.9)	3 (7.7)	5 (11.4)
Nasopharyngitis	8 (5.1)	9 (5.9)	1 (2.6)	2 (4.5)
Bronchitis	7 (4.4)	4 (2.6)	0	1 (2.3)
Gastroenteritis	4 (2.5)	3 (2.0)	2 (5.1)	1 (2.3)
Urinary Tract Infection	7 (4.4)	1 (0.7)	1 (2.6)	1 (2.3)
Influenza	4 (2.5)	3 (2.0)	0	0
Respiratory Tract Infection	2 (1.3)	3 (2.0)	0	0
Sinusitis	4 (2.5)	0	0	3 (6.8)
Nausea	3 (1.9)	4 (2.6)	0	0
Fatigue	4 (2.5)	2 (1.3)	0	0
Cough	5 (3.2)	2 (1.3)	0	0
Hypertension	4 (2.5)	7 (4.6)	0	0
Dyslipidaemia	4 (2.5)	0	0	0
Hepatic Enzyme Increased	1 (0.6)	0	0	3 (6.8)
Headache	3 (1.9)	3 (2.0)	1 (2.6)	1 (2.3)

[a]AEs reported in ≥2% of subjects 60-100 kg, and ≥2 subjects ≥100 kg (due to small subgroup size).

Includes data up to 56 days post the last dose in the ST Period or the first dose in the Open-label Period, whichever occurred first. MEDDRA VERSION: 18.0.

Overall, the proportions of female subjects with AEs were comparable, although incidence of some AEs were numerically higher in females; urinary tract infections were reported more frequently in females than males treated with abatacept. In general, individual AEs were reported by similar proportions of female and male subjects with no clinically relevant differences in AEs between the treatment groups in male and female subgroups (Table 24).

Table 24: AEs reported during the short term period by gender; As treated population

Preferred Term	Number of Subjects (%)[a]			
	Males		Females	
	Abatacept SC N=92	Placebo N=99	Abatacept SC N=121	Placebo N=112
Total Subjects with AEs	**41 (44.6)**	**41 (41.4)**	**75 (62.0)**	**71 (63.4)**
Upper Respiratory Tract Infection	2 (2.2)	5 (5.1)	4 (3.3)	9 (8.0)
Nasopharyngitis	2 (2.2)	1 (1.0)	7 (5.8)	10 (8.9)
Urinary Tract Infection	1 (1.1)	0	8 (6.6)	2 (1.8)
Gastroenteritis	5 (5.4)	3 (3.0)	2 (1.7)	2 (1.8)
Bronchitis	3 (3.3)	2 (2.0)	4 (3.3)	3 (2.7)
Sinusitis	0	0	4 (3.3)	3 (2.7)
Influenza	3 (3.3)	2 (2.0)	1 (0.8)	1 (0.9)
Conjunctivitis	0	0	3 (2.5)	1 (0.9)
Respiratory Tract Infection	1 (1.1)	2 (2.0)	1 (0.8)	1 (0.9)
Tooth Abscess	1 (1.1)	2 (2.0)	0	0
Nausea	0	1 (1.0)	3 (2.5)	4 (3.6)
Aphthous Stomatitis	1 (1.1)	0	2 (1.7)	2 (1.8)
Abdominal Pain	0	2 (2.0)	3 (2.5)	0
Diarrhea	1 (1.1)	1 (1.0)	1 (0.8)	3 (2.7)
Cough	1 (1.1)	0	4 (3.3)	3 (2.7)
Pyrexia	0	0	4 (3.3)	3 (2.7)
Fatigue	1 (1.1)	1 (1.0)	3 (2.5)	1 (0.9)
Oedema Peripheral	2 (2.2)	0	4 (3.3)	0
Muscle Spasms	0	0	3 (2.5)	1 (0.9)
Arthalgia	0	2 (2.0)	0	0
Back Pain	2 (2.2)	0	2 (1.7)	2 (1.8)
Hypertension	1 (1.1)	0	4 (3.3)	7 (6.3)
Headache	1 (1.1)	1 (1.0)	3 (2.5)	3 (2.7)
Dyslipidaemia	3 (3.3)	0	1 (0.8)	0
Hypertriglyceridaemia	2 (2.2)	0	0	1 (0.9)
Vertigo	2 (2.2)	0	1 (0.8)	2 (1.8)

[a] AEs reported in ≥2% of subjects.

Includes data up to 56 days post the last dose in the ST Period or the first dose in the Open-label Period, whichever occurred first. MEDDRA VERSION: 18.0

Extrinsic factors: Geographic regions, TNFi, MTX and oral steroid use

Overall, AEs were reported by similar proportions of subjects among the four geographic areas where the study was conducted (Europe, North America, South America, and Rest of the World). Europe was the only region where the proportion of subjects with infections was numerically higher for abatacept compared to placebo, whereas the reverse was true in North America and ROW. In general, individual AEs were reported by similar proportions of subjects across geographic regions (Table 25).

Table 25: AEs reported in at least 5% of subjects during the short-term period by geographic region; As treated population

PREFERRED TERM (PT) (%)	Abatacept SC (N=44)	Placebo (N=40)
Subgroup: Geographic Region: North America		
TOTAL SUBJECTS WITH AE	24 (54.5)	23 (57.5)
SINUSITIS	4 (9.1)	2 (5.0)
UPPER RESPIRATORY TRACT INFECTION	2 (4.5)	4 (10.0)
BRONCHITIS	2 (4.5)	1 (2.5)
NASOPHARYNGITIS	0	2 (5.0)
NAUSEA	1 (2.3)	3 (7.5)
CHEST PAIN	0	2 (5.0)
HEADACHE	0	2 (5.0)
Subgroup: Geographic Region: Europe		
TOTAL SUBJECTS WITH AE	29 (54.7)	29 (49.2)
NASOPHARYNGITIS	4 (7.5)	3 (5.1)
BRONCHITIS	3 (5.7)	2 (3.4)
PYREXIA	1 (1.9)	3 (5.1)
OEDEMA PERIPHERAL	3 (5.7)	0
Subgroup: Geographic Region: South America		
TOTAL SUBJECTS WITH AE	52 (54.7)	42 (52.5)
NASOPHARYNGITIS	5 (5.3)	3 (3.8)
URINARY TRACT INFECTION	5 (5.3)	1 (1.3)
Subgroup: Geographic Region: ROW		
TOTAL SUBJECTS WITH AE	11 (52.4)	18 (56.3)
UPPER RESPIRATORY TRACT INFECTION	2 (9.5)	6 (18.8)
GASTROENTERITIS	1 (4.8)	3 (9.4)
NASOPHARYNGITIS	0	3 (9.4)
HYPERTENSION	2 (9.5)	2 (6.3)

Includes data up to 56 days post the last dose in the short-term period or the first dose in the open-label period, whichever occurs first.

The frequencies of subjects with AEs overall and Infections and Infestations (the predominant SOC in both groups) were similar between concomitant MTX treatment (MTX-Yes) and no concomitant MTX treatment (MTX-No) groups Individual AEs were reported by similar proportions of subjects in the two groups with no clinically relevant differences in AEs between the treatment groups based on concomitant MTX use (Table 26). Similarly the frequencies of subjects with overall AEs and Infections and Infestations were similar between prior exposure to TNFi (TNFi-Yes) and TNFi-naïve (TNFi-No) groups. Individual AEs were generally reported by similar proportions of subjects in the two groups with no clinically relevant differences in AEs between the treatment groups based on prior TNFi exposure (Table 27).

Table 26: AEs reported in at least 2% of subjects during the short-term period by concomitant methotrexate use; As treated population

Subgroup :	MTX Use at Day 1 YES		MTX Use at Day 1 NO	
PREFERRED TERM (PT) (%)	Abatacept SC (N=129)	Placebo (N=127)	Abatacept SC (N=84)	Placebo (N=84)
TOTAL SUBJECTS WITH AE	65 (50.4)	68 (53.5)	51 (60.7)	44 (52.4)
NASOPHARYNGITIS	7 (5.4)	7 (5.5)	2 (2.4)	4 (4.8)
UPPER RESPIRATORY TRACT INFECTION	3 (2.3)	10 (7.9)	3 (3.6)	4 (4.8)
BRONCHITIS	4 (3.1)	5 (3.9)	3 (3.6)	0
GASTROENTERITIS	2 (1.6)	5 (3.9)	5 (6.0)	0
URINARY TRACT INFECTION	4 (3.1)	2 (1.6)	5 (6.0)	0
ORAL HERPES	3 (2.3)	2 (1.6)		
CONJUNCTIVITIS	3 (2.3)	1 (0.8)		
APHTHOUS STOMATITIS	3 (2.3)	2 (1.6)		
INFLUENZA			2 (2.4)	3 (3.6)
SINUSITIS			3 (3.6)	2 (2.4)
DIARRHOEA	2 (1.6)	3 (2.4)		
BACK PAIN			2 (2.4)	1 (1.2)
MUSCLE SPASMS			2 (2.4)	1 (1.2)
ARTHRALGIA			0	2 (2.4)
MUSCLE CONTRACTURE			2 (2.4)	0
NECK PAIN			0	2 (2.4)
NAUSEA			2 (2.4)	3 (3.6)
PYREXIA			3 (3.6)	1 (1.2)
FATIGUE			2 (2.4)	1 (1.2)
CHEST PAIN			0	2 (2.4)
OEDEMA PERIPHERAL	4 (3.1)	0	2 (2.4)	0
COUGH	3 (2.3)	2 (1.6)	2 (2.4)	1 (1.2)
DYSLIPIDAEMIA	3 (2.3)	0		
HEADACHE	3 (2.3)	2 (1.6)		
DEPRESSION	4 (3.1)	0		
HYPERTENSION	2 (1.6)	3 (2.4)	3 (3.6)	4 (4.8)
HEADACHE			1 (1.2)	2 (2.4)
PRURITUS			1 (1.2)	2 (2.4)
VERTIGO			2 (2.4)	1 (1.2)

Includes data up to 56 days post the last dose in the short-term period or the first dose in the open-label period, whichever occurred first.

Table 27: AEs reported for at least 2% of subjects during the short-term period by concomitant prior exposure to TNFi agents; As treated population

Subgroup:	TNF Exposed: YES		TNF Exposed: NO	
PREFERRED TERM (PT) (%)	Abatacept SC (N=129)	Placebo (N=130)	Abatacept SC (N=84)	Placebo (N=81)
TOTAL SUBJECTS WITH AE	75 (58.1)	66 (50.8)	41 (48.8)	46 (56.8)
NASOPHARYNGITIS	6 (4.7)	7 (5.4	3 (3.6)	4 (4.9)
URINARY TRACT INFECTION	7 (5.4)	2 (1.5)	2 (2.4)	0
UPPER RESPIRATORY TRACT INFECTION	3 (2.3)	5 (3.8)	3 (3.6)	9 (11.1)
GASTROENTERITIS	4 (3.1)	1 (0.8)	3 (3.6)	4 (4.9)
SINUSITIS	2 (1.6)	3 (2.3)	2 (2.4)	0
BRONCHITIS	1 (0.8)	3 (2.3)	6 (7.1)	2 (2.5)
RESPIRATORY TRACT INFECTION	1 (0.8)	3 (2.3)		
INFLUENZA			2 (2.4)	1 (1.2)
PHARYNGITIS			0	2 (2.5)
ABDOMINAL PAIN			2 (2.4)	1 (1.2)
NAUSEA	3 (2.3)	2 (1.5)	0	3 (3.7)
DIARRHOEA	1 (0.8)	3 (2.3)		
APHTHOUS STOMATITIS			2 (2.4)	0
STOMATITIS			0	2 (2.5)
COUGH	3 (2.3)	2 (1.5)	2 (2.4)	1 (1.2)
FATIGUE	4 (3.1)	1 (0.8)		
OEDEMA PERIPHERAL			4 (4.8)	0
PYREXIA	3 (2.3)	1 (0.8)	1 (1.2)	2 (2.5)
BACK PAIN			2 (2.4)	1 (1.2)
MUSCLE SPASMS			2 (2.4)	1 (1.2)
HYPERCHOLESTEROLAEMIA	3 (2.3)	1 (0.8)		
DYSLIPIDAEMIA	3 (2.3)	0		
HEPATIC ENZYME INCREASED			0	2 (2.5)
HYPERTENSION	1 (0.8)	6 (4.6)	4 (4.8)	1 (1.2)
DIABETES MELLITUS INADEQUATE CONTROL			0	2 (2.5)
CHOLELITHIASIS			0	2 (2.5)
HEADACHE	3 (2.3)	0	1 (1.2)	4 (4.9)
INSOMNIA	3 (2.3)	1 (0.8)		
DEPRESSION	3 (2.3)	0		
VERTIGO	3 (2.3)	1 (0.8)		

Includes data up to 56 days post the last dose in the short-term period or the first dose in the open-label period, whichever occurs first.

The frequencies of overall AEs and of Infections and Infestations were generally similar between subjects taking oral steroids versus those not taking oral steroids at Day 1 Individual AEs were generally reported by similar proportions of subjects in the two groups with no clinically relevant differences in AEs between the treatment groups based on concomitant oral steroid use (Table 28).

Table 28: AEs reported for at least 3% of subjects during the short-term period by concomitant oral steroid use; As treated population

Subgroup:	Oral Steroid Use at Day 1: YES		Oral Steroid Use at Day 1: NO	
PREFERRED TERM (PT) (%)	Abatacept SC (N=54)	Placebo (N=48)	Abatacept SC (N=155)	Placebo (N=163)
TOTAL SUBJECTS WITH AE	31 (57.4)	24 (50.0)	85 (53.5)	88 (54.0)
NASOPHARYNGITIS	5 (9.3)	3 (6.3)	4 (2.5)	8 (4.9)
UPPER RESPIRATORY TRACT INFECTION	1 (1.9)	5 (10.4)	5 (3.1)	9 (5.5)
BRONCHITIS	2 (3.7)	2 (4.2)	5 (3.1)	3 (1.8)
ACUTE SINUSITIS	0	2 (4.2)		
GASTROENTERITIS	2 (3.7)	0	5 (3.1)	5 (3.1)
URINARY TRACT INFECTION			8 (5.0)	1 (0.6)
NAUSEA			3 (1.9)	5 (3.1)
OEDEMA PERIPHERAL			6 (3.8)	0
PAROTID GLAND ENLARGEMENT	2 (3.7)	0		
MUSCLE SPASMS	2 (3.7)	1 (2.1)		
PYREXIA	2 (3.7)	0		
DEPRESSION	2 (3.7)	0		

Includes data up to 56 days post the last dose in the short-term period or the first dose in the open-label period, whichever occurred first.
MEDDRA VERSION: 18.0

Subgroup analysis of safety during the open label, long term extension phase of pivotal Study IM101332: Analyses were performed on AEs, SAEs and AEs of special interest for two subgroups: subjects with/without concomitant MTX use (that is, MTX-Yes and MTX-No) and subjects with/without prior exposure to TNFi inhibitors (that is, TNFi-exposed and TNFi-naive). The incidence ratios per 100 p-y for AEs, SAEs, and AEs of special interest had slightly higher incidence in patients not receiving concomitant MTX, although differences were small (Table 29).

Table 29: Incidence rates of AEs during the cumulative abatacept period up to Year 2 (double blind, open label, long term extension period) for MTX subgroup; Cumulative abatacept population

	ABATACEPT SC EXPOSURE			
	MTX-YES (N=247)		MTX-NO (N=151	
SYSTEM ORGAN CLASS (SOC) PREFERRED TERM (PT)	SUBJECTS WITH EVENT (%)	RATE: (INCIDENCE/100 (PERSON-YEARS)	SUBJECTS WITH EVENT (%)	RATE: (INCIDENCE/100 PERSON-YEARS)
TOTAL SUBJECTS WITH AE	168 (68.0)	142.53	109 (72.2)	187.59
TOTAL SUBJECTS WITH SAE	21 (8.5)	8.43	15 (9.9)	10.44
AEs OF SPECIAL INTEREST				
TOTAL SUBJECTS WITH INFECTIONS[a]	109 (44.1)	63.21	72 (47.7)	73.20
BRONCHITIS	22 (8.9)	9.12	9 (6.0)	6.27
UPPER RESPIRATORY TRACT INFECTION	19 (7.7)	7.82	14 (9.3)	9.98
NASOPHARYNGITIS	17 (6.9)	6.94	9 (6.0)	6.14
URINARY TRACT INFECTION	11 (4.5)	4.38	11 (7.3)	7.71
GASTROENTERITIS	5 (2.0)	1.96	10 (6.6)	6.93
INFLUENZA	11 (4.5)	4.43	8 (5.3)	5.39
TOTAL SUBJECTS WITH MALIGNANCIES	0 (0.0)	0.00	3 (2.0)	2.00
TOTAL SUBJECTS WITH AUTOIMMUNE EVENTS	1 (0.4)	0.35	1 (0.7)	0.66
TOTAL SUBJECTS WITH LOCAL INJECTION SITE REACTIONS	4 (1.6)	1.57	1 (0.7)	0.66
TOTAL SUBJECTS WITH AEs WITHIN 24 HR	61 (24.7)	29.16	41 (27.2)	35.83

a) Individual infection AEs reported at frequencies ≥ 5% are listed in this table
Includes data from the first day of the double blind period for subjects randomized and treated with abatacept and from the first day of Open-label Period for subjects randomized and treated with placebo up to 56 days post the last abatacept dose in the study.
Rate: (incidence/100 person-years) = number of subjects with event * 100 /exposure (person-years)
Exposure (person-years) = the sum over all subjects of the Abatacept exposure per subject in cumulative abatacept period up to Year 2 (censored at the time of first occurrence of AE) expressed in days, divided by 365.25.
For subjects who discontinue in the short-term, Open-label or long-term extension includes data up to 56 days post last abatacept dose in the study.
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Incidence rates for AEs, SAEs, and AEs of special interest were highest for Infections and Infestations in both groups. Incidence rates were generally similar between groups with respect to individual AEs. Similar results were observed in the previously exposed to TNFi (TNFi-Yes) versus TNFi-naive subjects (TNFi-No) subgroups (Table 30).

Table 30: Incidence rates of AEs during cumulative abatacept period up to Year 2 (double blind, open label, long term extension period) for TNFi subgroup; cumulative abatacept population

	ABATACEPT SC EXPOSURE					
	TNFi-YES (N=238)			TNFi-NO (N=160)		
SYSTEM ORGAN CLASS (SOC) PREFERRED TERM (PT)	SUBJECTS WITH EVENT (%)		RATE: (INCIDENCE/100 PERSON-YEARS)	SUBJECTS WITH EVENT (%)		RATE: (INCIDENCE/100 PERSON-YEARS)
TOTAL SUBJECTS WITH AE	152	(63.9)	163.98	125	(78.1)	150.10
TOTAL SUBJECTS WITH SAE	20	(8.4)	10.34	16	(10.0)	8.03
AEs OF SPECIAL INTEREST						
TOTAL SUBJECTS WITH INFECTIONS[a]	101	(42.4)	72.75	80	(50.0)	60.63
NASOPHARYNGITIS	18	(7.6)	9.47	8	(5.0)	3.97
UPPER RESPIRATORY TRACT INFECTION	15	(6.3)	7.91	18	(11.3)	9.30
URINARY TRACT INFECTION	15	(6.3)	7.92	7	(4.4)	3.42
BRONCHITIS	13	(5.5)	6.78	18	(11.3)	9.33
INFLUENZA	7	(2.9)	3.56	12	(7.5)	5.99
TOTAL SUBJECTS WITH MALIGNANCIES	2	(0.8)	1.01	1	(0.6)	0.48
TOTAL SUBJECTS WITH AUTOIMMUNE EVENTS	2	(0.8)	1.00	0		0
TOTAL SUBJECTS WITH LOCAL INJECTION SITE REACTIONS	3	(1.3)	1.51	2	(1.3)	0.96
TOTAL SUBJECTS WITH AE WITHIN 24 HR	59	(24.8)	36.85	43	(26.9)	26.30

[a] Individual Infection AEs reported at frequencies ≥ 5% are listed in this table.
Includes data from the first day of the double blind period for subjects randomized and treated with abatacept and from the first day of Open-label Period for subjects randomized and treated with placebo up to 56 days post the last abatacept dose in the study.
Rate: (incidence/100 person-years) = number of subjects with event * 100 /exposure (person-years)
Exposure (person-years) = the sum over all subjects of the Abatacept exposure per subject in cumulative abatacept period up to Year 2 (censored at the time of first occurrence of AE) expressed in days, divided by 365.25.
For subjects who discontinue in the short-term, Open-label or long-term extension includes data up to 56 days post last abatacept dose in the study.
MEDDRA VERSION: 18.0

Use in pregnancy/lactation

No pregnancies were reported in abatacept-treated subjects in pivotal Study IM101332. One pregnancy was reported in an abatacept-treated subject in the 3/3 mg/kg group during the short term period of Phase IIb Study IM101158. The patient was discontinued from the study and had an induced abortion. Pregnancies have been reported in studies conducted with abatacept in RA and no safety signals have been reported. The current product information indicates that abatacept should not be used in pregnant women unless the potential benefit to the mother outweighs the potential risk to the foetus. Women of child-bearing potential should use highly effective contraception during treatment with abatacept and up to 14 weeks after the last dose of abatacept treatment. Abatacept was excreted in rat milk. It is not known whether abatacept is excreted in human milk or absorbed systemically after ingestion by a nursing infant. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from abatacept, a decision should be made whether to discontinue breastfeeding or discontinue the drug.

Overdose, drug abuse, withdrawal/rebound, ability to drive/operate machinery

Two abatacept-treated subjects in the PsA studies had an SAE of overdose:

- One abatacept-treated subject in Study IM101332 had an SAE of accidental overdose (considered by the investigator to be related to abatacept therapy) during the long term extension period. The subject had two abatacept injections that were 2 days apart (5 January 2016 and 7 January 2016). The next injection was on 14 January 2016. No other AEs or SAEs were reported for this subject; she did not receive treatment for the accidental overdose and the overdose did not lead to discontinuation of abatacept treatment.
- One abatacept-treated subject in the abatacept 30/10 mg/kg group of Study IM101158, had an SAE of overdose of abatacept (considered by the investigator to be unrelated to abatacept) during the short term period. No other AEs or SAEs were reported for this subject; he did not receive treatment for this overdose and the overdose did not lead to discontinuation of abatacept treatment.

The PI indicates that doses of abatacept up to 50 mg/kg have been administered IV without apparent toxic effect.

The potential for drug abuse was not studied for abatacept. There is no evidence that suggests a risk for abuse or a potential for dependence. No studies on withdrawal or rebound after cessation of abatacept therapy have been performed in subjects with PsA. Results from two studies conducted in subjects with RA (Studies IM101226 and IM101167) indicated that withdrawal and subsequent reintroduction of SC abatacept therapy did not seem to impact the safety profile of the drug. No studies have been performed on the effects of abatacept treatment on the ability to drive or operate machinery.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction (DDI) studies have been performed for abatacept in subjects with active PsA; however, the current approved product information for abatacept states that concomitant use of abatacept with TNF antagonists or other biologic RA therapy is not recommended.

Post marketing experience

No periodic safety update reports (PSURs) were provided for evaluation in the current submission.

Abatacept is marketed in many countries worldwide for the treatment of moderately to severely active RA and for the treatment of JIA. Depending on the country or territory specific license, it may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists. The first marketing authorisation was granted to the sponsor on 23 December 2005 in the United States which was also the International Birth Date (IBD) and the harmonised birth date (HBD) for abatacept.

Clinical investigation of abatacept has been underway since 15 August 1995. As of 22 December 2015, approximately 10,771 subjects have been exposed to abatacept in sponsor sponsored clinical trials. The cumulative number of patients treated from 23 December 2005 through 30 September 2015 is estimated to be 383,451.

A comprehensive and detailed medical review of all safety and efficacy data/information currently available for abatacept, including review of safety signals, did not reveal a change to the well-established favourable benefit-risk profile of abatacept. The sponsor will continue to monitor the important identified and potential risks with abatacept therapy by routine pharmacovigilance activities and careful monitoring of subjects enrolled in ongoing or future trials.

Evaluator's conclusions on safety

The risks of abatacept in PsA were characterised in 594 subjects with PsA in two clinical studies.

Phase III Study IM101332 evaluated abatacept SC 125 mg weekly in 424 patients and Phase IIb Study IM101158 evaluated abatacept IV (3 dosing regimens) in 170 patients. The overall mean duration of exposure to abatacept in Study IM101332 was 10.8 months as of the last assessment and in Study IM101158, during the combined short term + long term period, the overall mean duration of exposure to abatacept was 20.4 months.

In the pivotal Study IM101332, abatacept 125 mg SC was well tolerated when administered weekly for 24 weeks. The safety of SC abatacept was similar to that of placebo with respect to percentages of subjects reporting total AEs (abatacept versus placebo: 54.5% versus 53.1%), SAEs (2.8% versus 4.3%), discontinuations due to AEs (1.4% versus 1.9%; 2.5% in open label phase) and AEs of special interest (Table 31).

Table 31: AEs of special interest reported during the short-term period; As treated population

	n (%) Abatacept SC (N=213)	Placebo (N=211)
TOTAL SUBJECTS WITH INFECTIONS AND INFESTATIONS	57 (26.8)	63 (29.9)
TOTAL SUBJECTS WITH MALIGNANCIES	0	2 (0.9)
TOTAL SUBJECTS WITH AUTOIMMUNE EVENTS	0	0
TOTAL SUBJECTS WITH LOCAL INJECTION SITE REACTIONS	1 (0.5)	1 (0.5)
TOTAL SUBJECTS WITH AE WITHIN 24 HR	39 (18.3)	39 (18.5)

Includes data up to 56 days post the last dose in the ST Period or the first dose in the Open-label Period, whichever occurred first.
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The incidence of treatment related AEs was higher in the abatacept SC group compared with placebo (15.5% versus 11.4%) with infections/infestations (8.6% versus 7.1%) being most common. During the open label, long term extension phase, the AE profile in subjects with PsA treated with abatacept for up to 2 years was consistent with the known AE profile of abatacept SC with the most common AEs being infections/ infestations (nasopharyngitis, bronchitis, upper respiratory tract infection and urinary tract infection).

In the Phase IIb Study IM101158, AEs were reported in similar percentage of subjects in the IV abatacept 30/10, 10/10, 3/3 mg/kg and placebo groups (67.4%, 77.5%, 68.9%, and 71.4%, respectively). The most frequently reported AEs were infection related events (for example, pharyngitis, nasopharyngitis, upper respiratory tract infection, bronchitis, sinusitis and tooth infection) with no apparent dose related trend. The only non-infection AEs that were reported at a rate that was approximately 2 times higher in an abatacept treatment group compared with placebo were fatigue and musculoskeletal chest pain. The incidence of treatment related AEs was higher in the abatacept IV groups (30.2%, 32.5% and 26.7% in 30/10, 10/10 and 3/3mg/kg groups, respectively) compared with placebo (16.7%) with infections/infestations being most common.

Administration of IV abatacept for up to 29 months in the long term period or up to 35 months across the short term and/or long term periods was generally safe and well tolerated in adult subjects with PsA.

There were no deaths in the short term and open label (interim data) of the pivotal Phase III study evaluating abatacept SC (162mg weekly) or in the Phase IIb Study IM101158 which evaluated IV abatacept.

In both studies, during the short term period, the frequencies of haematologic and clinical chemistry parameters that met the sponsor defined marked anomaly criteria was small (typically < 3%) and generally similar in the abatacept and placebo groups. Vital signs remained stable in both groups in both studies and ECG was not reported in either study.

In Study IM101158, few patients developed anti-drug antibodies following IV dosing, during the short term period. The immunogenicity rates in patients with PsA were 1 out of 43 (2.3%), 0 out of 40 (0), and 2 out of 45 (4.4%) following IV doses of 30/10 mg/kg, 10/10 mg/kg, and 3/3 mg/kg groups, respectively, and rates were similar to those previously determined for patients with RA. During the long term period, the overall abatacept-induced immunogenicity rate was 8.2% (12 out of 147), with an on-treatment immunogenicity rate of 3.4% (5 out of 145) and a post-treatment immunogenicity rate of 7.1% (9 out of 126). Medical review of the safety data among subjects with an abatacept-induced seropositive response in the long term period indicated that AEs were not consistent with immune mediated toxicities. Immunogenicity status did not appear to affect efficacy responses. Similarly, following SC dosing with abatacept in pivotal Study IM1010332, the incidence of abatacept immunogenicity rates were low during both

during the short term and the cumulative abatacept periods and rates were similar in both the abatacept and placebo treated groups. Overall, immunogenicity had no clear relationship with efficacy or safety and was consistent with what has been observed in the RA development program.

In pivotal Study IM101332, there was no clinically relevant difference in safety of abatacept SC (162 mg once weekly) based on weight (< and ≥100kg), gender, race or geographic region. Although incidence of AEs was slightly higher in the abatacept group compared to placebo in the subgroup > 65 years while incidence was similar in the subgroup < 65 years, interpretation was limited by small number of patients in the ≥ 65 years subgroup. The frequencies of subjects with AEs overall and Infections and infestations (the predominant SOC in both groups) were not affected by prior treatment with TNFi or concomitant treatment with MTX, or steroids.

Infections/infestations were the most commonly reported AEs (abatacept versus placebo: 26.8% versus 29.9%). Nasopharyngitis and upper respiratory infections were most common, and both of these AEs were reported slightly more frequently in the placebo group (5.2% and 6.6%, respectively) than in the abatacept group (4.2% and 2.8%, respectively). During the open label, long term extension phase, the AE profile in subjects with PsA treated with abatacept for up to 2 years was consistent with the known AE profile of abatacept SC. No subgroup analysis was done for safety of IV abatacept in the Phase IIb Study IM101158.

There was one reported opportunistic infection in an abatacept-treated subject in the pivotal Phase III study (a moderate Pneumocystis jirovecii infection which led to discontinuation from study). There did not appear to be any reports of tuberculosis although this was not clearly stated in the clinical study reports. There were 3 malignancies reported in Study IM101332 (none in short term period and 3 in open label phase in placebo-treated subject who switched to open label abatacept SC treatment) and 3 in Study IM101158 (1 in short term period in a subject treated with abatacept 30/10 mg/kg IV and 2 in the open label phase). All the reported malignancies were not serious and review of narratives suggest they were not treatment related.

Subjects who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines were excluded from the PsA studies. In view of the long half-life of abatacept, study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication. The proposed PI includes the following information which appears to be adequate: '*Live vaccines should not be given concurrently with Orencia or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving Orencia. No data are available on the effects of vaccinations in patients receiving Orencia. Drugs that affect the immune system, including Orencia, may blunt the effectiveness of some immunizations*.'

Abatacept, both SC and IV showed a comparable safety profile to placebo in subjects with PsA. Overall, the safety profile of abatacept in adults with active PsA was consistent with the previous clinical experience of abatacept in adults with RA. There were no new or unexpected safety signals.

First round benefit-risk assessment

First round benefit assessment

The following table describes the first round assessment of benefits.

Table 32: First round assessment of benefits

Benefits	Strengths and Uncertainties
Abatacept SC (125 mg weekly) treatment demonstrated statistically and clinically relevant efficacy in psoriatic arthritis in terms of primary endpoint of ACR20. Numerically better ACR50 and ACR70 response rates with abatacept SC. Efficacy of abatacept SC demonstrated as monotherapy and combination therapy with non-biologic DMARDs.	After 6 months of double blind treatment, ACR20 was 39.4% versus 22.3% in abatacept SC and placebo groups, respectively. Abatacept SC 125mg versus placebo: – ACR50: 19.2% versus 12.3%; – ACR70: 10.3% versus 6.6%. ACR20 of abatacept SC versus placebo: – with non-biologic DMARDs: 44.9% versus 26.9%; – without non-biologic DMARDs: 27.3% versus 12.1%. Very few subjects treated with non-MTX DMARDs.
Similar efficacy of abatacept in terms of ACR20 was observed in patients with prior TNFi exposure and those who were TNFi naïve.	ACR20 abatacept SC versus placebo in TNFi naïve subjects: 44% versus 22%; TNFi exposed subjects: 36% versus 22%. However, ACR20 response rates in the TNFi-naive and TNFi exposed subgroups could not be formally assessed for statistical significance due to failure to achieve significance higher in the statistical testing hierarchy in Phase III Study IM101332.
Improvements in physical function (HAQ)-with abatacept SC.	However, HAQ was the key secondary endpoint in the hierarchical analysis and failed to show statistically significant improvement over placebo in pivotal Study IM101332.
Extra-articular manifestations (enthesitis, and dactylitis) of PsA showed improvements with abatacept SC compared with placebo.	At Day 169: abatacept SC versus placebo: – Resolution of enthesitis: 32.9% versus 27.3% – Resolution of dactylitis: 44.3% versus 34%.
Modest non-significant improvements in psoriasis skin symptoms with abatacept SC compared with placebo.	PASI50 response rates abatacept versus placebo: 26.7% versus 19.6% with greater difference in TNFi naïve subjects (32.7% versus 19.6%) compared to TNF-exposed subjects (23.1% versus 19.6%).

Benefits	Strengths and Uncertainties
IV abatacept 30/10 and 10/10 mg/kg IV dosing regimens also showed statistically significant improvements over placebo in ACR20 response rate. ACR50 and ACR70 response rates numerically better than placebo with IV abatacept although interpretation limited by small number of patients. Minor improvements in enthesitis and dactylitis with abatacept IV.	ACR20 was 42%, 48%, 33% and 19% in IV abatacept 30/10, 10/10, 3/3 mg/kg and placebo groups, respectively. No additional benefit observed with higher initial (30 mg) IV dosing. Abatacept IV 10 mg/kg versus placebo: – ACR50: 25% versus 2.4%; – ACR70: 12.5% versus 0%. Efficacy of proposed IV abatacept was not evaluated in subgroups based on concomitant use of non-biologic DMARDs in Phase IIb study.
Larger proportion of subjects treated with abatacept SC were radiographic non-progressors, (defined as a change from baseline in total PsA modified Sharp/van der Heijde score ≤ 0, at Day 169 by X-ray) compared with placebo (42.7% versus 32.7%).	Evidence for prevention of structural damage by abatacept does not comply with EU guidelines for medicinal products for treatment of PsA, which states that slowing of radiographic progression may itself not constitute a definite patient benefit and it is still not accepted surrogate for long term clinical benefit. Confirmatory trials for prevention of structural damage are required to have observation period of at least 2 years showing sustained benefits are maintained after the first year. It is also recommended that a clinical efficacy co-primary endpoint is added to the radiological score primary endpoint.
Abatacept, both SC and IV, showed comparable safety profile to placebo in subjects with PsA. Safety results during open label, long term phase similar to that observed in short term phase of both studies.	Results from both studies indicate that the safety profile of abatacept is consistent with that of the previously established profile in subjects with RA. No new safety concerns were identified. Number of patients treated with proposed IV dosing was limited.

First round risk assessment

The following table describes the first round assessment of risks.

Table 33: First round assessment of risks

Risks	Strengths and Uncertainties
Increased risk of infections with abatacept treatment.	Low incidence with majority of infections mild to moderate intensity; < 2% serious infections leading to discontinuation in just 1.4% of abatacept treated patients.
Infusional AEs (IV only) or injection related AEs (SC only).	Very low incidence with no discontinuations due to these AEs.

Risks	Strengths and Uncertainties
Potential increased risk of opportunistic infections, malignancies, autoimmune disorders, hypersensitivity.	Very low incidence.
Risk of development of anti-drug antibodies.	Overall, 7 to 8% of subjects developed anti-drug antibodies with higher immunogenicity post-treatment; positive antibody response not associated with AEs or effect on abatacept efficacy.
Proposed IV dosing was only evaluated in the Phase IIb dose-ranging Study IM101158. No Phase III study evaluated efficacy/ safety of proposed IV abatacept.	In Phase IIb study which was also the first study to evaluate abatacept in treatment of PsA, only 40 patients treated with proposed abatacept IV 10/10 mg/kg during the double blind, controlled short term 6 month period.
Efficacy of proposed IV abatacept was not evaluated in subgroups based on concomitant use of non-biologic DMARDs. Limited evidence of efficacy of abatacept IV in both TNFi-naïve and TNFi-experienced patients.	In the Phase II study which evaluated IV abatacept, only a post hoc analysis of efficacy in subgroups based on prior TNFi status was conducted and interpretation was limited further as randomisation was not stratified based on prior use of TNFi.
Very modest efficacy of IV abatacept on symptoms of psoriasis; Phase II study showed minimal improvements with proposed abatacept IV 10/10 mg/kg with greatest improvements observed in the abatacept IV 3/3 mg/kg.	It is also important to note that the open label long term extension phase of the Phase IIb study was terminated due to modest effects on psoriasis.
Proposed dosing of abatacept SC is weekly.	Other recently approved therapies in Australia for treatment of PsA require less frequent dosing and comparable efficacy (with better effects on psoriasis), such as ustekinumab (45 mg administered by subcutaneous injection at Weeks 0 and 4, then every 12 weeks thereafter), secukinumab (150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4) and apremilast (30 mg twice daily taken orally approximately 12 hr apart).

First round assessment of benefit-risk balance

The efficacy and safety of abatacept were assessed in two randomised, double blind, placebo controlled studies in 594 adult patients with active PsA (> 3 swollen and tender joints) and active psoriasis (defined as at least one qualifying skin lesion > 2 cm in diameter) despite prior treatment with DMARD therapy. This was representative of the target patient population.

Following either 10 mg/kg IV doses every four weeks (in Study IM101158) or weekly doses of 125 mg SC (in Study IM101332), the C_{min} values at steady state were similar resulting in abatacept concentrations >10 µg/mL which are associated with the therapeutic efficacy of abatacept in patients with RA. The Phase IIb Study IM101158 with IV abatacept (3/3, 10/10 and 30/10 mg/kg) showed that near maximal efficacy in terms of ACR20 was achieved with the 10/10 mg/kg weight-tiered monthly regimen, and no greater efficacy was shown with inclusion of 2 loading doses of 30 mg/kg IV (30/10 mg/kg).

Treatment with abatacept SC (125 mg weekly) and abatacept IV (10 mg/kg) resulted in a statistically significantly higher proportion of subjects with PsA achieving an ACR20 response at Day 169 compared with placebo in both studies. In addition, a numerically higher proportion of subjects in the abatacept group compared to the placebo group achieved ACR50 and ACR70 responses at Day 169 in both studies although interpretation for IV abatacept was limited by small number of patients treated with proposed dose. Abatacept treatment was associated with improvements in arthritis, enthesitis, dactylitis, spinal symptoms, and psoriasis, assessed individually and within composite measures. Abatacept treatment was associated with greater improvements in synovitis, oedema, and erosion as assessed by MRI in Study IM101158 at Day 169, and fewer subjects with radiographic progression of x-rays in Study IM101332 at Day 169 in the abatacept than in the placebo groups. However, evidence for inhibition of structural damage was not adequate as radiographic non-progression is not considered evidence of prevention of structural damage according to EU guidelines which also recommend that a clinical efficacy co-primary endpoint is added to the radiological score primary endpoint which was not done in the abatacept PsA studies.

During the open label period of the pivotal Phase III study, efficacy was maintained or improved for the subjects who remained on abatacept SC, and improved for the subjects who transitioned from placebo to abatacept.

Both Studies IM101158 and IM101332 included subjects who had been previously exposed to TNFi as well as TNFi naive subjects. In Study IM101332, 61% of subjects had prior TNFi exposure while in Study IM101158, 37% of subjects had a history of TNFi use. In both studies, although results tended to be better for the TNFi-naive population, abatacept showed numerically greater ACR20 response rates compared with placebo in both TNFi naive and TNFi exposed subgroups. However, ACR20 response rates in the TNFi-naive and TNFi exposed subgroups could not be formally assessed for statistical significance due to failure to achieve significance higher in the statistical testing hierarchy in Phase III Study IM101332. It is also important to note that in the Phase IIb study (only study which evaluated proposed IV abatacept) only a post hoc analysis of ACR20 and ACR50 response rates was done based on prior use of TNFi and interpretation was limited by small number and fact that randomisation as not stratified by prior TNFi use.

Higher ACR20 responses in the Phase III Study IM101332 were seen with abatacept 125 mg SC versus placebo irrespective of concomitant non-biologic DMARD treatment. The ACR20 responses with Orencia 125 mg SC versus placebo in patients who did not use non-biologic DMARDs was 27.3% versus 12.1% (difference =15.15, 95% confidence interval (CI): 1.83 to 28.47) and it was 44.9% versus 26.9% (18.00, 95%CI: 7.20 to 28.81) in patients who had used non-biologic DMARDs. Hence, efficacy of proposed abatacept SC

125 mg weekly was shown as monotherapy and in combination with non-biologic DMARDs in patients with active PsA. However, the Phase IIb study (only study which evaluated proposed IV abatacept) did not provide analysis of ACR20 response rates with abatacept IV 10 mg/kg irrespective of concomitant non-biologic DMARD treatment. Hence, there is no evidence to support use of IV abatacept as monotherapy or in combination with non-biologic DMARDs.

Both Studies IM101158 and IM101332 showed modest non-significant benefit on psoriasis. The modest effects on psoriasis were observed across multiple endpoints, including PASI (objective assessment on subjects with at least 3% body surface area involvement at baseline), target lesion score (objective assessment on all subjects), and in Study IM101332, the DLQI (dermatology life quality index) assessment of patient reported quality of life. Benefits observed at the 6 month analysis were maintained during the open label periods in both studies. No new forms of psoriasis developed in response to abatacept treatment in the controlled periods of the two studies. However, the evidence for benefit in psoriasis symptoms with proposed IV abatacept was inadequate. In the Phase IIb study, IV abatacept showed better response for psoriasis with the 3 mg/kg dose compared to the proposed 10 mg/kg dose. Furthermore, the long term phase of Phase IIb study was terminated early due to modest effect on psoriasis.

The risks of abatacept in PsA were characterised in 594 subjects with PsA in two clinical studies. The overall mean duration of exposure to abatacept in Study IM101332 was 10.8 months up to the 1 year database lock. In Study IM101158, during the combined short term and long term period, the overall mean duration of exposure to abatacept was 20.4 months although the number of patients treated with abatacept IV was much lower than those who received abatacept SC. The safety of abatacept in RA, using the same doses as in PsA, is well documented.

Abatacept, both SC and IV, shows a comparable safety profile to placebo in subjects with PsA. Furthermore, results from both studies confirm that the safety profile of abatacept is consistent with that of the previously established profile in subjects with RA. There was no increased incidence of malignancies or opportunistic infections in the two PsA studies. Immunogenicity had no clear relationship with efficacy or safety and was consistent with what has been observed in the RA development program. There was no increased risk for immunogenicity or AEs in the absence of MTX therapy in subjects with PsA. Long term safety results for abatacept in both studies were consistent with the safety results in the short term period. No new signals or clinically significant safety information arose from the PsA studies.

Currently approved effective therapies in PsA include biologic DMARDs such as TNFi (adalimumab, etanercept, infliximab, golimumab, and certolizumab), an IL-12/23 inhibitor (ustekinumab), an IL-17 antagonist (secukinumab), and an oral inhibitor of phosphodiesterase 4 (apremilast) (Tables 34, 35). None of the abatacept studies directly compared abatacept with an approved PsA treatment and cross-study comparison is difficult due to differences in study design, target populations, geographic differences, and analysis methods used in published results. The pivotal Phase III PsA Study IM101332 included one of the highest proportions of patients with prior TNFi use (61%). The next highest proportion of TNFi experienced subjects was included in one study of ustekinumab[22] which differed from the abatacept studies. Overall, abatacept has demonstrated clinically relevant efficacy in the articular domain comparable to other approved therapies for PsA (Table 34).

[22] Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73:990-999.

Table 34: ACR20 responses for abatacept and recently approved therapies for PsA

Agent	Study	Dose	TNFi-exposed subjects	Agent		Placebo		Effect size (ACR 20 agent - ACR 20 placebo)
				n	ACR 20 (%)	n	ACR 20 (%)	
Abatacept	IM101158	10 mg/kg IV	37%	40	47.5	42	19.0	28.5
	IM101332	125 mg SC	61%	213	39.4	211	22.3	17.1
Apremilast	PALACE-1, 2, 3 pooled*	30 mg BID	22%	497	37.0	496	18.8	18.2
Secukinumab	PsA Study 2 (without IV loading)	150 mg SC	35%	100	51.0	98	15.3	35.7
		300 mg SC	35%	100	54.0	98	15.3	38.7
Ustekinumab	Study 1	45 mg SC	0%	205	42.4	206	22.8	19.6
		90 mg SC	0%	204	49.5	206	22.8	26.7
	Study 2	45 mg SC	58%	103	43.7	104	20.2	23.5
		90 mg SC	58%	105	43.8	104	20.2	23.6

*Week 16 data
n is the number of subjects treated

Table 35: ACR20 responses for abatacept and recently approved therapies for PsA – TNFi naïve subjects

Agent	Target	Study	Dose	Agent		Placebo		Effect size (ACR 20 agent - ACR 20 placebo)
				n	ACR 20 (%)	n	ACR 20 (%)	
Abatacept	CD80/86	IM101158	10 mg/kg IV	27	55.6	30	20.0	35.6
		IM101332	125 mg SC	84	44	81	22.2	21.8
Certolizumab	TNF	RAPID-PsA	400 mg SC/month	219	60.3	110	26.4	33.9
Apremilast	PDE4	PALACE-1*	30 mg BID	120	43	118	24	19
Secukinumab	IL-17	PsA Study 2	150 mg SC	63	63	63	16	47
		(without IV loading)	300 mg SC	67	58	63	16	42
Ustekinumab	IL-12/23p40	Study 1	45 mg SC	205	42.4	206	22.8	19.6
			90 mg SC	204	49.5	206	22.8	26.7
		Study 2	45 mg SC	43	53.5	42	28.6	24.9
			90 mg SC	47	55.3	42	28.6	26.7

*Week 16 data
n is the number of subjects treated

Abatacept could provide a new therapeutic choice for patients with PsA by offering a novel mechanism of action in this disease. Abatacept could potentially provide physicians with the option of treating patients with abatacept after failure of a non-biologic DMARD prior to treatment with other DMARD/biologic therapies with different or less established safety profiles. The data presented from the two studies also provided some evidence to support the use of abatacept after failure of a TNFi in patients with PsA.

However, the efficacy of abatacept with respect to psoriasis in PsA is modest compared with other biologic therapies currently approved for PsA. Furthermore, some of the other drugs that are approved for treatment of PsA in Australia require less frequent dosing and comparable efficacy (with better effects on psoriasis) such as ustekinumab (45 mg administered by SC injection at Weeks 0 and 4, then every 12 weeks thereafter), secukinumab (150 mg by SC injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4) and apremilast (30 mg twice daily taken orally approximately 12 hr apart). Therefore, the sponsors suggest '*that abatacept SC is likely to be most appropriate for patients with predominantly articular and musculoskeletal manifestations of PsA*'; however, this was not specifically evaluated in this submission.

Despite the above limitation, the submission provides adequate evidence to support efficacy and safety of abatacept SC dose for the proposed indication. Hence, the benefit risk profile for abatacept (SC) is favourable for the following proposed indication: '*treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs*'.

However, the benefit risk profile for abatacept (IV) is unfavourable for the following proposed indication- '*treatment of active psoriatic arthritis (PsA) in adults when the*

response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs'.

First round recommendation regarding authorisation

Approval of abatacept SC (125mg weekly) is recommended for the proposed indication of:

> *Orencia is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs*.

The above approval for SC abatacept is subject to satisfactory response to clinical questions and incorporation of suggested changes to proposed PI.

However, approval of abatacept (Orencia) IV is not recommended for proposed indication:

> *Orencia is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs.*

The main reasons for rejection of proposed IV dosing with abatacept are as follows:

- Proposed IV dosing with abatacept not evaluated adequately; only 40 patients received proposed dose of 10 mg/kg IV in the controlled, double blind phase of the Phase IIb study which was also the first ever study to evaluate abatacept for treatment of PsA. The efficacy/ safety of proposed IV dosing with abatacept was not evaluated in a Phase III study.
- There is no evidence to support use of IV abatacept as monotherapy or in combination with non-biologic DMARDs. The Phase IIb study (only study which evaluated proposed IV abatacept) did not provide analysis of ACR20 response rates with abatacept IV 10 mg/kg based on concomitant non-biologic DMARD treatment.
- Phase IIb study only did post hoc analysis of efficacy (abatacept IV versus placebo) in subgroups based on prior TNFi status and interpretation was limited due to small numbers and fact that randomisation was not stratified based on prior TNFi use.
- The efficacy of abatacept with respect to psoriasis in PsA is modest with no statistically significant improvements. In the Phase IIb study, abatacept IV 3 mg/kg showed better improvements in symptoms of psoriasis compared to the proposed 10 mg/kg dose. Furthermore, the long term phase of Phase IIb study was terminated early due to modest effect on psoriasis.

Second round evaluation

The following is a summary of the sponsor's responses to the Clinical questions and the evaluator's comments on the sponsor's responses.

Efficacy

Question 1

The proposed indication in draft PI submitted in EU is: '*Orencia is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate*.'

The proposed indication in the draft PI submitted in US is: '*Orencia is indicated for the treatment of adult patients with active psoriatic arthritis (PsA). Orencia may be used as monotherapy or concomitantly with DMARDs.'*

However, the proposed US indication provided with this submission is as follows:

'*Orencia is indicated for the treatment of adult patients with active psoriatic arthritis (PsA). Orencia can be used with or without non-biologic DMARDs*.'

The proposed Australian indication is as follows:

'*Orencia is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs.'*

The sponsors have been asked to clarify the slight difference in text mentioned in the submission to that provided in the draft US PI.

There is no statement in the submission which explicitly states that a submission for application of Orencia for proposed PsA indication has not been rejected or withdrawn. Could the sponsors confirm this?

Sponsor response

The sponsor has clarified that in the draft US PI there was an unintended inconsistency between the proposed text of the PsA indication in the 'Highlights of Prescribing Information' and the proposed text of the PsA indication in the Full Prescribing Information.

The sponsors have also informed that based on the completed FDA review of the PsA submission, the approved PsA indication in the US (date of approval: 30 June 2017) no longer includes any reference to concomitant medications, as shown below: Final 'Highlights of Prescribing Information' states: 'Adult Psoriatic Arthritis (PsA) (1.3) active PsA in adults.(1.3)' Final 'Full Prescribing Information' states: '1.*3 Adult Psoriatic Arthritis (PsA) Orencia is indicated for the treatment of adult patients with active psoriatic arthritis (PsA).*'

The initially proposed indication in the EU has been reviewed by the Committee for Medicinal Products for Human Use (CHMP), and has evolved during the procedure. On 22 June 2017, the CHMP adopted a positive opinion recommending the following indication for the treatment of PsA. '*Orencia, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy including MTX has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required*.' EU approval is expected at the end of August 2017.

The sponsor confirms that there have been no deferrals, withdrawals or rejections for the proposed PsA indication for Orencia.

Evaluator comments

The sponsor's response is satisfactory.

Question 2

The reports for both Studies IM101158 and IM101332 did not specify if patients with each type of PsA (polyarticular arthritis; spondylitis with peripheral arthritis; asymmetric peripheral arthritis, distal interphalyngeal involvement) were enrolled in the study. The sponsors are requested to provide this information.

Sponsor response

PsA is a remarkably heterogeneous disease. This is exemplified by the original Moll and Wright subtype definitions for PsA[23]: 1) oligoarticular, affecting 4 or fewer joints, typically in an asymmetric distribution, 2) polyarticular, affecting 5 or more joints, often in a symmetric distribution, 3) distal subtype, which affects the distal interphalangeal joints of the hands and/or feet, usually occurring with other subtypes, 4) arthritis mutilans, a deforming and highly destructive subtype, and 5) spondylitis, primarily involving the axial joints. Because these subtypes can change over time and multiple subtypes can be present concurrently, these descriptions have not been useful when selecting therapy for a particular patient. More recently, treatment recommendations have been developed based on the presence and severity in each individual PsA patient of different domains of disease,[24] namely, 1) peripheral arthritis, 2) axial disease, 3) enthesitis, 4) dactylitis, 5) skin disease, and 6) nail disease. These disease domains formed the basis of the clinical assessments performed in both Study IM101332 and Study IM101158, in order to inform physicians regarding the efficacy of abatacept for treatment of the different manifestations of PsA.

In both Studies IM101158 and IM101332 the type of PsA based on the Moll and Wright criteria was not collected. Both studies enrolled mostly patients with polyarticular arthritis based on the mean/median number of tender joints and of swollen joints; for Study IM101158, 22.2/19.0 and 10.9/9.0 tender and swollen joints, respectively and for Study IM101332, 20.2/17.0 and 11.6/9.0 tender and swollen joints, respectively. In Study IM101332, 98% of subjects had polyarticular disease based on the joint counts 5 and 50.7% had involvement of the distal interphalangeal joints. Axial involvement such as spondylitis was not assessed by radiographic analysis in either study. In Study IM101332, 100 out of 213 (46.9%) in the abatacept group and 84 out of 211 (39.8%) in the placebo group had a BASDAI score of at least 4, a cut-off shown to differentiate disease activity in patients with axial PsA compared with patients with peripheral PsA.

Evaluator comments

The sponsor's response is satisfactory.

Question 3

In pivotal Study IM101332, almost all patients had prior use of non-biologic DMARDs (68.6%, 23.1% and 6.6% had used 1, 2 or > 3 non-biologic DMARDs). However, details regarding use of non-biological DMARDs other than MTX were not provided in the study report. Subjects who have been treated with apremilast within 4 weeks, ustekinumab within 20 weeks, or briakinumab within 8 weeks prior to randomization were excluded from the study, but details were not provided regarding how many subjects had received prior treatment with these agents and whether they were non-responders. Details regarding use of biological DMARDs other than TNFis especially ustekinumab, secukinumab and apremilast (which are approved for treatment of PsA in Australia) were not provided. Did any of the patients receive prior treatment with these agents and were they not responsive to these?

Sponsor response

MTX was the most commonly used non-biologic DMARD prior to randomisation (94.8% in the abatacept group and 91.9% in the placebo group). Prior use of leflunomide (19.2% in the abatacept group and 13.3% in the placebo group) and sulfasalazine (18.3% in the abatacept group and 21.8% in the placebo group) were also reasonably common. No randomised subjects reported using apremilast prior to randomisation, although it is

23 Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. N Engl J Med 2017; 376:957-970.
24 Coates L, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol 2016;68(5):1060-71.

possible that it could have been captured under 'investigational immunotherapy' based on the timing of the start of Study IM101332. Two subjects in the abatacept group and 1 subject in the placebo group reported prior use of ustekinumab, but no subjects specifically reported prior use of briakinumab or secukinumab (unless reported as 'investigational immunotherapy'). A single subject was reported to have been exposed to tocilizumab and a single subject to rituximab, both from the placebo group. The response of subjects to ustekinumab, tocilizumab, and rituximab has not been specifically analysed given the low number of subjects previously exposed to these therapies.

Evaluator comment

The sponsor's response is satisfactory.

Question 4

The report for the Phase IIb Study IM101158 did not provide any information regarding the mean change from baseline in each of the ACR core set components for the primary efficacy endpoint.

Sponsor response

In support of the efficacy findings for Study IM101158, a post hoc analysis was performed examining the mean change from baseline in the ACR core components over time.

The mean change from baseline in all of the individual ACR core components was numerically greater in the abatacept 10 mg/kg group than the placebo group at all time-points, up to and including Day 169.

Evaluator comment

The sponsor's response is satisfactory.

Safety

Question 5

There did not appear to be any reports of tuberculosis although this was not clearly stated in the study report. Could the sponsors confirm this?

Sponsor response

No cases of active tuberculosis were reported during either Study IM101158 or Study IM101332

Evaluator comment

The sponsor's response is satisfactory.

Second round benefit-risk assessment

Second round benefit assessment

After consideration of the responses to clinical questions, the benefits of Orencia in the proposed usage are unchanged from First round benefit assessment in Table 32 above.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Orencia in the proposed usage are described in Table 36.

Table 36: Second round assessment of risks

Risks	Strengths and Uncertainties
Increased risk of infections with abatacept treatment.	Low incidence with majority of infections mild to moderate intensity; < 2% serious infections leading to discontinuation in just 1.4% of abatacept treated patients.
Infusional AEs (IV only) or injection related AEs (SC only).	Very low incidence with no discontinuations due to these AEs.
Potential increased risk of opportunistic infections, malignancies, autoimmune disorders, hypersensitivity.	Very low incidence.
Risk of development of Anti-drug antibodies.	Overall, 7 to 8% of subjects developed anti-drug antibodies with higher immunogenicity post-treatment; positive antibody response not associated with AEs or effect on abatacept efficacy.
Proposed IV dosing was only evaluated in the Phase IIb dose-ranging Study IM101158. No Phase III study evaluated efficacy/ safety of proposed IV abatacept.	Comparable PK Cminss exposures were delivered by proposed IV and SC abatacept dosing regimens. The observed efficacy response (ACR20 treatment effect) for the proposed IV and SC dosing regimens was also comparable.
Very modest efficacy of IV abatacept on symptoms of psoriasis; Phase II study showed minimal improvements with proposed abatacept IV 10/10 mg/kg with greatest improvements observed in the abatacept IV 3/3 mg/kg.	It is also important to note that the open label, long term extension phase of the Phase IIb study was terminated due to modest effects on psoriasis.
Proposed dosing of abatacept SC is weekly.	Other recently approved therapies in Australia for treatment of PsA require less frequent dosing and comparable efficacy (with better effects on psoriasis), such as ustekinumab (45 mg administered by subcutaneous injection at Weeks 0 and 4, then every 12 weeks thereafter), secukinumab (150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4) and apremilast (30 mg twice daily taken orally approximately 12 hr apart).

Second round assessment of benefit-risk balance

The benefit-risk balance of Orencia given the proposed usage is favourable.

The efficacy and safety of abatacept were assessed in two randomised, double blind, placebo controlled studies in 594 adult patients with active PsA (> 3 swollen and tender joints) and active psoriasis (defined as at least one qualifying skin lesion > 2 cm in diameter) despite prior treatment with DMARD therapy. This was representative of the target patient population.

Treatment with abatacept SC (125 mg weekly) and abatacept IV (10 mg/kg) resulted in a statistically significantly higher proportion of subjects with PsA achieving an ACR20 response at Day 169 compared with placebo in both studies. In addition, a numerically higher proportion of subjects in the abatacept group compared to the placebo group achieved ACR50 and ACR70 responses at Day 169 in both studies although interpretation for IV abatacept was limited by small number of patients treated with proposed dose. Abatacept treatment was associated with improvements in arthritis, enthesitis, dactylitis, spinal symptoms, and psoriasis, assessed individually and within composite measures. Abatacept treatment was associated with greater improvements in synovitis, oedema, and erosion as assessed by MRI in Study IM101158 at Day 169, and fewer subjects with radiographic progression of x-rays in Study IM101332 at Day 169 in the abatacept than in the placebo groups. During the open label period of the pivotal Phase III study up to 1 year efficacy was maintained or improved for the subjects who remained on abatacept SC, and improved for the subjects who transitioned from placebo to abatacept. However, evidence for inhibition of structural damage was not adequate with limited evidence of non-progression but no evidence on effect on structural damage beyond 1 year.

Both Studies IM101158 and IM101332 included subjects who had been previously exposed to TNFi as well as TNFi naive subjects. In Study IM101332, 61% of subjects had prior TNFi exposure while in Study IM101158, 37% of subjects had a history of TNFi use. In both studies, although results tended to be better for the TNFi-naive population, abatacept showed numerically greater ACR20 response rates compared with placebo in both TNFi naive and TNFi exposed subgroups. However, ACR20 response rates in the TNFi-naive and TNFi exposed subgroups could not be formally assessed for statistical significance due to failure to achieve significance higher in the statistical testing hierarchy in Phase III Study IM101332. It is also important to note that in the Phase IIb study (only study which evaluated proposed IV abatacept) only a post hoc analysis of ACR20 and ACR50 response rates was done based on prior use of TNFi and interpretation was limited by small number and fact that randomisation as not stratified by prior TNFi use.

Higher ACR20 responses in the Phase III Study IM101332 were seen with abatacept 125 mg SC versus placebo irrespective of concomitant non-biologic DMARD treatment. The ACR20 responses with Orencia 125 mg SC versus placebo in patients who did not use non-biologic DMARDs was 27.3% versus 12.1% (difference = 15.15, 95% CI: 1.83 to 28.47) and it was 44.9% versus 26.9% (18.00, 95%CI: 7.20 to 28.81) in patients who had used non-biologic DMARDs. Hence, efficacy of proposed abatacept SC 125 mg weekly was shown as monotherapy and in combination with non-biologic DMARDs in patients with active PsA.

Both Studies IM101158 and IM101332 showed modest non-significant benefit on psoriasis. The modest effects on psoriasis were observed across multiple endpoints, including PASI (objective assessment on subjects with at least 3% body surface area involvement at baseline), target lesion score (objective assessment on all subjects), and in Study IM101332 the DLQI assessment of patient reported quality of life. Benefits observed at the 6 month analysis were maintained during the open label periods in both studies. No new forms of psoriasis developed in response to abatacept treatment in the controlled periods of the two studies. However, the evidence for benefit in psoriasis symptoms with

proposed IV abatacept was inadequate. In the Phase IIb study, IV abatacept showed better response for psoriasis with the 3 mg/kg dose compared to the proposed 10 mg/kg dose. Furthermore, the long term phase of Phase IIb study was terminated early due to modest effect on psoriasis. Hence, it may be prudent to limit use of abatacept in PsA to patients in whom additional systemic therapy for psoriatic skin lesions is not required.

Following either 10 mg/kg IV doses every four weeks (in Study IM101158) or weekly doses of 125 mg SC (in Study IM101332), the C_{min} values at steady state were similar resulting in abatacept concentrations >10 µg/mL which are associated with the therapeutic efficacy of abatacept in patients with RA. The Phase IIb Study IM101158 with IV abatacept (3/3, 10/10 and 30/10 mg/kg) showed that near maximal efficacy in terms of ACR20 was achieved with the 10/10 mg/kg weight-tiered monthly regimen, and no greater efficacy was shown with inclusion of two loading doses of 30 mg/kg IV (30/10 mg/kg). Comparability between IV and SC abatacept was demonstrated in PsA from the following perspectives: (1) Comparable PK C_{minss} exposures were delivered by proposed IV and SC abatacept dosing regimens. (2) Comparable efficacy response rate (ACR20) following the proposed IV and SC abatacept dosing regimens was predicted by exposure-response model-based simulations. (3) The observed efficacy response (ACR20 treatment effect) for the proposed IV and SC dosing regimens was comparable.

The risks of abatacept in PsA were characterised in 594 subjects with PsA in two clinical studies. The overall mean duration of exposure to abatacept in Study IM101332 was 10.8 months up to the 1 year database lock. In Study IM101158, during the combined short term and long term period, the overall mean duration of exposure to abatacept was 20.4 months although the number of patients treated with abatacept IV was much lower than those who received abatacept SC. The safety of abatacept in RA, using the same doses as in PsA, is well documented.

Abatacept, both SC and IV, shows a comparable safety profile to placebo in subjects with PsA. Furthermore, results from both studies confirm that the safety profile of abatacept is consistent with that of the previously established profile in subjects with RA. There was no increased incidence of malignancies or opportunistic infections in the two PsA studies. Immunogenicity had no clear relationship with efficacy or safety and was consistent with what has been observed in the RA development program. There was no increased risk for immunogenicity or AEs in the absence of MTX therapy in subjects with PsA. Long term safety results for abatacept in both studies were consistent with the safety results in the short term period. No new signals or clinically significant safety information arose from the PsA studies.

Currently approved effective therapies in PsA include biologic DMARDs such as TNFi (adalimumab, etanercept, infliximab, golimumab, and certolizumab), an IL-12/23 inhibitor (ustekinumab), an IL-17 antagonist (secukinumab), and an oral inhibitor of phosphodiesterase 4 (apremilast) (Tables 33, 34). None of the abatacept studies directly compared abatacept with an approved PsA treatment and cross-study comparison is difficult due to differences in study design, target populations, geographic differences, and analysis methods used in published results. The pivotal Phase III PsA Study IM101332 included one of the highest proportions of patients with prior TNFi use (61%). The next highest proportion of TNFi experienced subjects was included in one study of ustekinumab;[22] which differed from the abatacept studies. Overall, abatacept has demonstrated clinically relevant efficacy in the articular domain comparable to other approved therapies for PsA (Table 33).

Abatacept could provide a new therapeutic choice for patients with PsA by offering a novel mechanism of action in this disease. Abatacept could potentially provide physicians with the option of treating patients with abatacept after failure of a non-biologic DMARD prior to treatment with other DMARD/biologic therapies with different or less established

safety profiles. The data presented from the 2 studies also provided some evidence to support the use of abatacept after failure of a TNFi in patients with PsA.

However, the efficacy of abatacept with respect to psoriasis in PsA is modest compared with other biologic therapies currently approved for PsA. Furthermore, some of the other drugs that are approved for treatment of PsA in Australia require less frequent dosing and comparable efficacy (with better effects on psoriasis) such as ustekinumab (45 mg administered by subcutaneous injection at Weeks 0 and 4, then every 12 weeks thereafter), secukinumab (150 mg by SC injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4) and apremilast (30 mg twice daily taken orally approximately 12 hr apart). The clinical overview also states '*that abatacept SC is likely to be most appropriate for patients with predominantly articular and musculoskeletal manifestations of PsA'*; however, this was not specifically evaluated in this submission. Hence, due to modest effect on psoriasis, it may be prudent to limit use of abatacept in PsA to patients in whom additional systemic therapy for psoriatic skin lesions is not required.

Despite the above limitation, the submission provides adequate evidence to support efficacy and safety of abatacept for the proposed indication. Hence, the benefit risk profile for abatacept (SC and IV formulation) is favourable for the following proposed indication: 'treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs. '

Second round recommendation regarding authorisation

Approval of abatacept (SC and IV formulations) is recommended for the proposed indication of:

> *Orencia is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs.*

The above approval for abatacept is subject to satisfactory response to comments in concerning the PI.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[25]

- The sponsor has submitted EU Risk Management Plan (RMP) version 21.0 (date 27 September 2016; data lock point (DLP) 22 April 2016) and ASA version 8 (date 11 November 2016) in support of this application.
- Following the second round RMP evaluation, the sponsor submitted an updated EU RMP version 23.0 (date 11 May 2017; DLP 30 June 2016) and an ASA version 9 (date 19 September 2017).
- The most recently evaluated EU RMP was version 16.1 (date 17 July 2014) and ASA version 7 (7 January 2015).

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 37.

Table 37: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infections with special reference to TB and patients with COPD	ü	ü*	ü	ü
	Infusion related reactions (IV abatacept only)	ü	ü*	ü	ü
	Injection reactions (SC abatacept only) Prefilled syringe Autoinjector	ü	ü*	ü	ü
Important potential risks	Malignancies, with special reference to lymphoma, NMSC, lung cancer, and breast cancer	ü	ü*	ü	–
	Autoimmune symptoms and disorders	ü	ü*	ü	–
	Immunogenicity	ü	ü*	ü	–
	Pregnancy	ü	ü#	ü	–

[25] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Administration error (SC abatacept only) Prefilled syringe Autoinjector	ü	–	ü	–
	Infections associated to immunization with live vaccines	ü	–	ü	ü
Missing information	Hepatic and renal impairment	ü	–	ü	–
	Combination therapy including biologic therapy	ü	ü*	ü	–
	Elderly subjects	ü	ü*	ü	–

*Clinical (epidemiological) trials # Pregnancy registry

Additional pharmacovigilance activities include clinical trials and a pregnancy registry. Additional risk minimisation activities include Patient Alert Card.

New and outstanding recommendations from the second round RMP evaluation

The sponsor has stated that the follow-up forms will not be appended to the ASA;[26] as these forms are included in the EU RMP. This is acceptable.

The sponsor has also stated that '*BMS does not plan to append the updated patient alert card to the ASA however, a copy of the updated patient alert card will be provided to the TGA when available*'. While the sponsor's justification for not appending the patient alert card to the ASA is acknowledged, it is reiterated that the sponsor should provide a copy of the updated patient alert card to the TGA prior to launch of the product. There were no changes to the summary of safety concerns in the updated EU RMP version 23.0 (date 11 May 2017; DLP 30 June 2016) and ASA version 9 (date 19 September 2017) provided with after the second round evaluation responses. There are no major changes to the pharmacovigilance and risk minimisation plans in these updated documents.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

Orencia (abatacept rch) has been previously considered by TGA's advisory committee in August 2007 for the initial registration of RA in adult patients and in 2009 for the extension of indications to polyarticular juvenile idiopathic arthritis in children and adolescents.

[26] ASA Pharmacovigilance Activities for Safety Concerns Specific to Australia

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval for the proposed indication subject to satisfactory response to comments regarding the product information.

Pharmacokinetics

The absolute bioavailability of the SC formulation of abatacept relative to the IV form has been previously reported to be 78.6%. The steady-state levels of abatacept were attained by Day 57 for both 10/10 mg/kg IV dose and 125 mg SC dose. After achieving the steady state the $C_{min,ss}$ remained consistent over time for the SC dose. The mean C_{min} values for abatacept following IV dosing were dose related. Consistent with previous results in RA patients, population PK analyses for abatacept in PsA patients identified that there was a trend toward higher abatacept clearance as body weight increased. In addition, relative to the RA patients with the same body weight, abatacept clearance in PsA patients was approximately 8% lower, resulting in slightly higher abatacept $C_{max,ss}$ and $C_{av,ss}$ but not $C_{min,ss}$ values in patients with PsA. Given the magnitude of the difference in clearance between the two diseases, and the exposure-response analyses identifying C_{minss} as the best exposure measure for predicting pharmacodynamic responses, this difference is unlikely to be clinically significant. The estimated central volume, peripheral volume, inter-compartmental clearance and clearance values were 3.2 L, 4.0 L, 0.025 L/h and 0.020 L/h, respectively.

Pharmacodynamics

In patients with PsA, immunogenicity rates following administration of IV or SC abatacept were low. For instance, following 10 mg/kg IV dosing every 4 weeks or weekly SC doses of 125 mg, 0% and 3.9% of patients, respectively, were identified as screening positive for anti-drug antibodies (ADAs).Pharmacometric analyses of data taken from a mixed population of patients with RA or PsA identified that increases in abatacept exposure (based on $C_{min,ss}$) were positively correlated with efficacy response (measured by ACR20/50/70 and PASI), which was similar to the population of patients with RA only.

Stochastic simulations predicted that following administration of either 125 mg SC or 10 mg/kg IV, steady-state trough concentrations of 11.8 µg/mL and 8.5 µg/mL or higher, would be attained in 95% of PsA patients, respectively, regardless of body weight. Graphical analysis of the relationship between steady-state exposures and AEs showed no clear association between abatacept exposure and safety. Overall the results indicate that both weekly SC administration of 125 mg abatacept or 10 mg/kg IV dosing every four weeks result in similar and effective improvements in ACR20 and PASI50 scores at 6 months.

Efficacy

Based on the therapeutic equivalence of abatacept 125 mg SC weekly to 10/10 mg/kg IV monthly dose of abatacept in RA and the comparison of pharmacokinetic results to the IV formulation in PsA in Study IM01158, a fixed-dose, 125 mg weekly SC abatacept regimen

was selected for studying the efficacy and safety in subjects with PsA in Study IM101332. Abatacept SC was administered without an IV loading dose in the pivotal Phase III Study IM101332. The proposed IV abatacept dose of 10 mg/kg was only evaluated in 40 subjects in the Phase IIb dose-ranging Study IM101158. No Phase III study was conducted with the proposed IV abatacept dose.

Study IM101332

This was a 24 week (169 days), Phase III, randomised, double blind, placebo controlled, multicentre study, followed by a 28 week (196 days) open label period (OL) and a 52 week long term (lt) extension in subjects with active PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR) and active psoriasis (at least 1 psoriasis lesion ≥ 2 cm in diameter). It included subjects aged > 18 years with a diagnosis of PsA, active arthritis as shown with ≥ 3 swollen joints and ≥ 3 tender joints at screening and randomisation/Day 1 who had an inadequate response or intolerance to at least one non-biologic (prior to study drug administration). At least one of the swollen joints must be in the digit of the hand or foot. DMARDs including MTX were allowed in the study. If currently on a non-biologic DMARDs (methotrexate (maximum of 25 mg weekly)) it must have been used for at least 3 months with a stable dose for at least 28 days and oral corticosteroids dose (≤ 10 mg/day prednisone equivalent), must have been stable ≥ 14 days. The main exclusion criteria were: an active systemic inflammatory condition other than PsA (for example, systemic lupus erythematosus); subjects who discontinued a non-biologic DMARD or systemic retinoid within four weeks or five half-lives prior to randomisation (Day 1) whichever is longer; subjects who have failed more than two TNFi agents (inadequate response after 3 months of treatment at a therapeutic dose).

Subjects were randomised in a 1:1 ratio to 125 mg SC weekly of abatacept (abatacept SC was administered without an IV loading dose) or placebo, including subjects with and without prior TNFi exposure. Randomisation was stratified globally by current MTX use, prior use of TNFi therapy, and for psoriasis involving > 3% of the skin body surface area (BSA). Up to approximately 40% of subjects with < 3% body surface area psoriatic skin involvement were planned to be randomised. A hierarchical testing procedure was applied for the primary endpoint (proportion of ACR20 responders at Day 169) and the 4 key secondary endpoints (proportion of HAQ responders, proportion of ACR20 responders in the TNFi subgroups, and proportion of non-progressors in total SHS at Day 169) to ensure the preservation of the overall type I error. All 424 (abatacept n = 213; placebo n = 211) randomised subjects received at least 1 dose of double blind study drug in the treatment period; 197 subjects in the abatacept group and 185 subjects in the placebo group entered the open label period.

The majority of subjects were White (92.7%) and female (55%). The overall mean age was 50.4 years (range: 22 to 81 years); mean duration of disease was 8.3 and 8.8 years in the abatacept and placebo groups, respectively, with 21.1% and 20.9% respectively having PsA for ≤ 1year. Baseline demographics and prior use of DMARDs, topical and systemic steroids and TNFi use were similar between the two groups. Overall, 60.6% of subjects in the abatacept group and 61.6% of subjects in the placebo group had previously taken TNFi. Non-biological DMARD was previously taken by 98.6% of subjects in the abatacept group and 98.1% in the placebo group. Methotrexate was the most commonly used (94.8% in the abatacept group and 91.9% in the placebo group. Prior use of leflunomide (19.2% in the abatacept group and 13.3% in the placebo group) and sulfasalazine (18.3% in the abatacept group and 21.8% in the placebo group) were the next common.

Overall, few patients received rescue medication during the short term period. The number of patients receiving systemic steroids (oral), localised steroids (intramuscular (IM), intra-articular (IA) or entheseal), or topical steroids was higher in the placebo group compared to the abatacept group. The most frequently reported concomitant anti-rheumatic medications (NSAIDs and DMARDs) were taken by similar proportions of

subjects in the abatacept and placebo groups at baseline and during the short term period up to the last dose. The mean baseline MTX weekly dose was 17.1 mg in both the arms and the mean oral daily steroid (prednisone equivalent) was 6.8 mg in the abatacept arm and 6.3 mg in the placebo arm.

The primary endpoint was proportion of ACR20 responders at Day 169. A statistically significantly higher proportion of subjects in the abatacept group compared with placebo met the criteria for ACR20 response at Day 169 (39.4% versus 22.3%, p < 0.001). Please refer to Table 38 below.

Table 38: ACR20 responders at Day 169 in Phase III Study IM101332

Endpoint (Day 169)	Abatacept N = 213	Placebo N = 211
Primary Endpoint		
ACR 20 response		
Subjects, n/N (%)	84/213 (39.4)	47/211 (22.3)
95% CI	32.9, 46.0	16.7, 27.9
Estimate of Difference (95% CI); p-value	17.2 (8.7, 25.6); <0.001	

Note: Early Escape subjects switching to open-label abatacept at Day 113 and other subjects with missing data at Day 169 of the double-blind ST Period were imputed as non-responders for the ACR 20 analyses up to Day 169. .

Subgroup analysis of ACR20 response by age, weight, body mass index (BMI), gender, race, geographic region, duration of disease, MTX use, non-biologic DMARD use, and steroid use showed ACR20 responses were numerically higher in the abatacept group compared to the placebo group in subgroups tested, with the exception of the < 60 kg-subjects in the intention to treat (ITT) population. The ACR20 responses with Orencia 125 mg SC versus placebo in patients who did not use non-biologic DMARDs was 27.3% versus 12.1% (difference = 15.15, 95% CI: 1.83 to 28.47) and it was 44.9% versus 26.9% (18.00, 95%CI: 7.20 to 28.81) in patients who had used non-biologic DMARDs. The proportion of subjects with ACR20 response was 44.2% (abatacept group) and 29.1% (placebo group) (15.05, 95%CI (3.40 to 26.71)) in the MTX use subgroup while it was 32.1% (abatacept group) and 11.9% (placebo group) (20.24, 95%CI (8.08 to 32.39) in the no MTX use group.

The results of the key secondary endpoints at Day 169, in hierarchical order are as below. Although the proportion of HAQ responders was numerically higher in the abatacept group than the placebo group (31% versus 23.7%), the difference was not statistically significant (difference = 7.2, 95% CI: -1.1 to 15.6, p = 0.097). Hence, none of the lower hierarchical secondary endpoint could be tested at the 5% significance level.

Other secondary endpoints at day 169 were:

- Proportion of subjects achieving a PASI50 in subjects with baseline body surface area > 3%. The proportion of subjects that achieved at least 50% improvement in Psoriasis Area and Severity Index (PASI50) scores at Day 169 was non-significantly higher in the abatacept group versus the placebo group (26.7% versus 19.6%, difference = 7.3, 95% CI: -2.2 to16.7, p = 0.137). This was numerically higher in the abatacept group versus the placebo group both in TNFi-naive (32.7% versus 19.6%) and TNFi exposed subpopulation (23.14% versus 19.6%).
- Proportions of ACR50 and ACR70 responders. Numerically higher proportion of subjects in the abatacept group, compared to the placebo group, met the criteria for an ACR50 (19.2% versus 12.3%) and ACR70 (10.3% versus 6.6%) response at Day 169 when Early Escape/missing subject data was imputed as non-responders. The proportion of subjects who met the criteria for ACR50 and ACR70 responses was numerically higher in the abatacept group versus the placebo group for the TNFi-exposed and TNFi-naive sub-populations. All efficacy assessments in the open label

period were exploratory endpoints. The results of the open label phase up to 1 year showed that treatment responses on joint signs and symptoms (ACR20/50/70, Dermatology life quality index (DLQI), MDA), psoriasis (PASI50/75), physical function (HAQ), other musculoskeletal changes (LEI, LDI and number of dactylitic digits), composite measures and health related QOL were maintained from the 6 month assessment through the 1 year assessment and improvements were seen in the placebo group upon switching to open label abatacept. Regardless of the original randomisation group, most subjects did not progress in the PsA modified SHS once abatacept treatment was started during the open label.

Study IM101158

This was a Phase IIb, multi-dose, multicentre, randomised, double blind, placebo controlled study to evaluate the efficacy and safety of abatacept versus placebo in the treatment of PsA. It consisted of two study periods: a 6 month double blind, placebo controlled short term period and an open label long term extension period for subjects who completed the short term period. Subjects were included in the study if they were men or women (not nursing or pregnant) ≥ 18 years of age who met CASPAR criteria for PsA and who had a tender joint count ≥ 3, a swollen joint count ≥ 3, and clinically detectable synovitis at screening and on Day 1 (prior to infusion); had active psoriasis with a qualifying target lesion of ≥ 2 cm in diameter; exhibited prior failure of DMARD therapy (lack of efficacy or intolerability).

Subjects with PsA were stratified by percentage of psoriasis-affected body surface area (BSA ≥ 3% versus < 3 %) and randomised on Day 1 in a 1:1:1:1 ratio to treatment with IV abatacept at 30/10 mg/kg (that is, 30 mg/kg on Days 1 and 15 followed by 10 mg/kg on Days 29, 57, 85, 113, and 141), 10/10 mg/kg or 3/3 mg/kg or placebo on Days 1, 15, 29 and every 28 days thereafter.

Subjects who entered the study on MTX were allowed to remain on this drug at a stable dose. Use of any other DMARD during the study was prohibited.

Efficacy analyses for the short term period were based on all randomised and treated subjects. Analyses of safety, immunogenicity, and efficacy were descriptive in nature and based on as-observed data. Of the 170 randomised and treated subjects in the short term period, 147 subjects completed the short term period, and the completion rate was higher for the abatacept treatment groups (95.6%, 85.0% and 86.0% for abatacept 3/3, 10/10 and 30/10 mg/kg groups, respectively) than for the placebo group (78.6%). Of the 23 subjects across all treatment groups who were discontinued during the short term period, the most common reasons for withdrawal were AEs (n = 7; 4.1%) and lack of efficacy (n = 10; 5.9%).

The majority of the patients were male (53.5%), White (97.6%) and enrolled in North America (57.1%). The mean age of patients was 51.3 years (range: 26 to 82 years) and mean weight was 89.7 kg (range 49 to 149.7 kg). Baseline demographics were similar across treatment groups in the short term period. The mean duration of PsA was 8.2 years. General medical history findings were consistent with active PsA and were balanced across the treatment groups. Most subjects had a history of MTX use prior to enrolment (69.0% to 85.0% across the 4 treatment groups) and approximately 60% of subjects in each treatment group were receiving MTX at enrolment (range: 57.1% to 60.0%). NSAIDs were the second most common anti-rheumatic drug class used at enrolment (range: 54.8% to 71.1%). Other DMARDs were received by 5.0% to 8.9% of the subjects at enrolment and which were azathioprine, hydroxychloroquine, leflunomide and sulfasalazine. The estimated mean daily oral corticosteroid dose at enrolment ranged from 5.8 to 7.3 mg across the three abatacept groups and was 6.8 mg in the placebo group. Overall 37% had a history of anti-TNF biologic use, and was more common for subjects randomised to the abatacept 30/10 mg/kg group (51.2%) and ranged from 28.6 to 35.6%

for the other three treatment groups. The mean oral dose for the abatacept 10/10 mg/kg group at screening was 1.7 mg as compared to 1.3 mg in the placebo group. No subject was receiving biologic therapy at enrolment into the study. The median duration of exposure to study drug in the short term period was 168 days for each of the four treatment groups, consistent with the planned 6 month duration of this period.

The primary efficacy endpoint of the short term period was to compare the efficacy of three regimens of abatacept (30/10 mg/kg, 10/10 mg/kg and 3/3 mg/kg) versus placebo as measured by the proportion of subjects achieving an ACR20 response at Day 169. The response was similar for abatacept 30/10 (42%) and abatacept 10/10 (48%) treatment groups with both showing statistically significant improvement over placebo (19%; p = 0.022 and p = 0.006, respectively). Although numerically greater than placebo (19%), the response rate for abatacept 3/3 mg/kg (33%) treatment group was not statistically significantly different (p = 0.121). Pre-specified subgroup analyses of primary efficacy endpoint were conducted for those subgroup categories which represented at least 20% of the total Randomised and Treated subject populations. Results were generally consistent in showing larger ACR20 response rates at Day 169 for the abatacept 30/10 mg/kg and abatacept 10/10 mg/kg group compared with placebo for the following subgroups: < 65 years of age, female subjects > 50 years of age, gender, White subjects, region of North America and other regions, baseline psoriasis BSA of < 3% and ≥ 3%, baseline dactylitis score ≤ 20%, and baseline enthesitis score ≤ 6%.

Secondary study efficacy endpoints for the short term period were to estimate the difference between each of the three abatacept treatment groups and placebo at Day 169 with regards to the following:

- The proportion of subjects with Investigator Global Assessment (IGA) response of clear or almost clear at Day 169 was highest for abatacept 3/3 mg/kg group (37.8%, 17 out of 45) in comparison to similar lower rates for the abatacept 30/10 mg/kg (20.9%, 9 out of 43), abatacept 10/10 mg/kg (25%, 10 out of 40) and placebo (26.2%, 11 out of 42) groups.
- Skin responses based on target lesion scoring showed numerically larger improvements at Day 169 for each of the abatacept treatment groups than for placebo with abatacept 3/3 mg/kg group (30.48%) being more than the abatacept 30/10 mg/kg (18.77%) and abatacept 10/10 mg/kg (22.34%) groups.
- In all 3 abatacept groups, the adjusted mean changes from baseline at Day 169 were > 3 points for both SF-36 component scores, physical and mental, (improvements of > 3 points are considered clinically relevant in patients with RA). At Day 169, the placebo adjusted differences demonstrated a difference of 6.17 to 7.15 in all three abatacept treatment groups in the PCS component of SF-36.
- The proportion of subjects with a diminution in disabilities as measured by HAQ scores at Day 169, defined as at least a 0.3 unit improvement from baseline in the HAQDI score, was higher for all three abatacept groups (34.9%, 45% and 35.6% for 30/10, 10/10 and 3/3 mg groups, respectively) than for the placebo group (19.0%).

ACR50, ACR70 and DAS28-CRP results were consistently higher in the abatacept groups compared with the placebo group for these exploratory endpoints.

Results for the completed open label, long term study period

Each of the 147 treated subjects who completed the short term period entered the long term period and received at least 1 infusion of open label abatacept. Approximately half of the 147 subjects treated in the long term period were discontinued for administrative reasons related to termination of the study by the sponsor (n = 76, 51.7%). Lack of efficacy (34.0%) was the second most common reason for discontinuation. In general, in the cohorts of subjects who received the abatacept 30/10 mg/kg or 10/10 mg/kg regimens

during the short term period, the data from the long term period are supportive of maintained treatment effect for abatacept with respect to arthritis. In the cohorts of subjects who received abatacept 3/3 mg/kg or placebo, in general the arthritis response improved during the long term period following initiation of treatment with abatacept 10 mg/kg. With respect to psoriasis in the long term period, the treatment effect was in general maintained during the long term period (relative to the end of the short term period) in all three abatacept cohorts, and improved in the placebo cohort. However, the open label, long term phase of this study was terminated early due to modest effects on psoriasis skin symptoms.

Safety

The safety of abatacept in PsA was characterised in 594 subjects with PsA in two clinical studies: Phase III Study IM101332 evaluated abatacept SC 125mg weekly in 424 patients and Phase IIb Study IM101158 evaluated abatacept IV (three dosing regimens) in 170 patients. The overall mean duration of exposure to abatacept in Study IM101332 was 10.8 months as of the last assessment and in Study IM101158, during the combined short term and long term period, the overall mean duration of exposure to abatacept was 20.4 months.

In the Phase III Study IM101332, during the short term period, frequencies of subjects with AEs were similar between groups (54.5% and 53.1% in abatacept and placebo groups, respectively). There were no deaths in the short term and open label (interim data) of the pivotal Phase III study Infections and infestations were the most commonly reported AEs (abatacept versus placebo: 26.8% versus 29.9%). Nasopharyngitis and upper respiratory infections were most common, and both of these AEs were reported slightly more frequently in the placebo group (5.2% and 6.6%, respectively) than in the abatacept group (4.2% and 2.8%, respectively). There was one reported opportunistic infection in an abatacept-treated subject in the pivotal Phase III study (a moderate *Pneumocystis jirovecii* infection which led to discontinuation from study). There were no cases of active tuberculosis reported. The incidence of treatment related AEs was higher in the abatacept SC group compared with placebo (15.5% versus 11.4%) with infections/infestations (8.6% versus 7.1%) being most common. During the open label, long term extension phase, the AE profile in subjects with PsA treated with abatacept for up to 2 years appears consistent with the known AE profile of abatacept SC. During the short term period, SAEs were reported in 6 subjects (2.8%) in the abatacept group and 9 subjects (4.3%) in the placebo group, with infections and infestations predominating in both groups. One (1) subject in each treatment group was reported with an SAE that was considered by the investigator to be related to study drug and resulting in treatment discontinuation. During the open label, long term extension phase, SAEs were reported in 36 subjects (9%). Serious infections were the most prevalent class of SAEs (8 subjects (2.0%)). Five SAEs (in 5 subjects (1.3%)) considered by the investigator to be related to abatacept included a moderate *Pneumocystis jirovecii* infection which was reported to have discontinued treatment due to the SAE at the time of database lock.

During the short term period, discontinuation of treatment due to AEs was reported in 1.4% and 1.9% of subjects in the abatacept and placebo groups, respectively. During the open label, long term extension phase, 10 subjects (2.5%) exposed to abatacept discontinued therapy due to AEs. Of the AEs leading to discontinuation, *Pneumocystis jirovecii infection* (SAE in the short term period) and pruritus (AE in the open label period) were considered related to abatacept. During the short term period, marked elevations in hepatic enzymes were noted in < 1% of subjects in the abatacept group and < 2% of subjects in the placebo group. One (1) subject in the placebo group was reported with an SAE of increased ALT on Day 63 9245 U/L) that was considered related to the drug by the investigator and resulted in treatment discontinuation. During the open label, long term

extension phase, markedly abnormal increases ranging from 2.3% to 3.0% of subjects were noted in AST, ALT and GGT.

In the Phase IIb Study IM101158, AEs were reported in similar percentage of subjects in the IV abatacept 30/10, 10/10, 3/3 mg/kg and placebo groups (67.4%, 77.5%, 68.9%, and 71.4%, respectively). There were no deaths. The most frequently reported AEs were infection related events (for example, pharyngitis, nasopharyngitis, upper respiratory tract infection, bronchitis, sinusitis and tooth infection) with no apparent dose related trend. The only non-infection AEs that were reported at a rate that was approximately two fold higher in an abatacept treatment group compared with placebo were fatigue and musculoskeletal chest pain. The incidence of treatment related AEs was higher in the abatacept IV groups (30.2%, 32.5% and 26.7% in 30/10, 10/10 and 3/3 mg/kg groups, respectively) compared with placebo (16.7%) with infections/infestations being most common. During the short term period, SAEs were reported by 4 (9.3%) subjects in the abatacept 30/10 mg/kg group, 2 subjects (5.0%) in the abatacept 10/10 mg/kg group, 1 subject (2.4%) in the placebo group, and no subject in the abatacept 3/3 mg/kg group for the all treated subjects population. Two subjects treated with abatacept experienced a total of 2 SAEs that were considered to be at least possibly related to study drug by the investigator All reported SAEs resolved during the short term period except for the events of osteomyelitis which led to discontinuation and basal cell carcinoma which resolved in the long term period (both in abatacept 30/10 mg/kg group). A total of 20 (13.6%) All Treated Subjects in long term period population experienced SAEs during the long term period while receiving abatacept at a weight-tiered dose of 10 mg/kg. SAEs during the long term period assessed as related to study drug were reported for 4 subjects (2.7%) (cellulitis, herpes zoster, pneumonia, acute pyelonephritis, and cardiac failure). None of the SAEs reported during the long term period led to discontinuation of abatacept. During the short term period, AEs led to the discontinuation of study drug during the short term period for 7 subjects, including 1 subject (2.3%) in the abatacept 30/10 mg/kg group, 2 subjects (5.0%) in the abatacept 10/10 mg/kg group, 1 subject (2.2%) in the abatacept 3/3 mg/kg group, and 3 subjects (7.1%) in the placebo group. During the long term period, treatment with abatacept was discontinued in 4 subjects (2.7%) due to an AE. One subject in the abatacept 30/10 mg/kg group had a marked elevation in ALT during the short term period. Markedly elevated ALT and AST values were reported during the long term period for 1 subject each (0.7%).

In both studies, during the short term period, the frequencies of haematologic and clinical chemistry parameters that met the sponsor defined marked anomaly (MA) criteria was small (typically < 3%) and generally similar in the abatacept and placebo groups. Vital signs remained stable in both groups in both studies and ECG was not reported in either study.

In Study IM101158, Immunogenicity rates (measured by development of anti-drug antibodies) in patients with PsA were 1 out of 43 (2.3%), 0 out of 40 (0), and 2 out of 45 (4.4%) following IV doses of 30/10 mg/kg, 10/10 mg/kg, and 3/3 mg/kg groups, respectively, and rates appeared similar to those previously determined for patients with RA. During the long term period, the overall abatacept induced immunogenicity rate was 8.2% (12 out of 147), with an on-treatment immunogenicity rate of 3.4% (5 out of 145) and a post-treatment immunogenicity rate of 7.1% (9 out of 126). Similarly, following SC dosing with abatacept in pivotal Study IM1010332, the incidence of abatacept immunogenicity rates were low during both during the short term and the cumulative abatacept periods and rates were similar in both the abatacept and placebo treated groups. Overall, immunogenicity did not appear to have a clear relationship with efficacy or safety.

RMP

The RMP evaluator has accepted the EU RMP for Orencia (abatacept), version 21.0 (dated 27 September 2016, DLP 22 April 2016), with the Australian Specific Annex, version 8 (dated 11 November 2016).

The RMP evaluator has accepted the sponsor's assurance it will incorporate the remaining recommendations into the next update of the ASA and Patient alert card (PAC).

The sponsor in their second round response have stated that they do not want to append the PAC or AE follow-up forms to the ASA, but have committed to supplying the PAC directly to the RMP team. This response from the sponsor appears acceptable to the RMP evaluator. These will be followed up by the RMP evaluator.

Risk-benefit analysis

In monoarticular or oligoarticular PsA disease, NSAIDs and intra-articular corticosteroid injections are often used first line; DMARDs are used for resistant or progressive cases. The DMARDs used are Conventional synthetic DMARDs (csDMARDs), Biological DMARDs (bDMARDs) and Targeted synthetic DMARDs (tsDMARDs)

Efficacy

The efficacy of abatacept in adult patients with active PsA (> 3 swollen and tender joints) and active psoriasis (defined as at least one qualifying skin lesion > 2 cm in diameter) despite prior treatment with DMARD therapy has been satisfactorily demonstrated up to 24 weeks in a pivotal study and a Phase IIb study and was maintained in the open label extension phase of the pivotal study up to 1 year. These studies are representative of the intended target patient population in Australia. The design and the efficacy parameters used are broadly consistent with other similar studies and the EU guideline on treatment of PsA and are considered acceptable.

A treatment dose of abatacept SC (125 mg weekly) was used in the pivotal study and abatacept IV (10 mg/kg) in the Phase IIb study to achieve the primary objective of the study, with statistically significantly higher proportion of subjects with PsA achieving an ACR20 response at Day 169 compared with placebo.

In the pivotal Phase III study the 'proportion of HAQ responders' at Day 169, which was first of the four key hierarchically ordered secondary endpoints, was numerically higher in abatacept group than the placebo group but not statistically significant. In the rest of the three key secondary endpoints that is, the ACR20 response rates in the TNFi-naive and TNFi exposed subgroups and proportion of X-ray non-progressors in total PsA modified SHS2 the proportion of subjects treated with abatacept were higher than placebo. HAQ response was also numerically better in the Phase IIb study. A numerically higher proportion of subjects in the abatacept group compared to placebo achieved ACR50, ACR70 and DAS28-CRP responses in both pivotal and Phase IIb studies.

In the pivotal Phase III study at Day 169 there were fewer abatacept subjects with radiographic progression on X-rays. The effect on structural damage was not evaluated beyond 1 year.

There was improvement seen in arthritis, dactylitis, enthesitis, spinal symptoms and psoriasis, which was measured through individual and composite endpoints in both studies. However, the long term phase of Phase IIb study was terminated early due to modest effect on psoriasis and the evidence of benefit for the IV dose appears inadequate. Considering this, the evaluator's recommendation to limit the use of abatacept to patients for whom additional systemic therapy for psoriatic skin lesions is not required seems reasonable. This has been added in the precaution section of the PI.

The comparability which was demonstrated between the proposed IV and SC abatacept dosing regimen in PsA was based on comparable pharmacokinetic C_{minss} exposures, comparable efficacy response rate (ACR20) and comparable observed efficacy responses. This appears reasonable. Although Phase IIb study has its limitations and the abatacept IV dosing not evaluated adequately, based on its comparability with the SC dosing (making the extrapolation of data from the SC to the IV presentation) the IV dosing appears to have a favourable benefit-risk profile. However, the proposed abatacept IV dosing for PsA in the PI (based on body weight) is an extrapolation and was not tested in the clinical trials and has been proposed by the sponsor to maintain consistency with the RA IV dosing. This is also the case with the US PI and the European Summary of product characteristics (SmPC).

In the pivotal Phase III study the ACR20 responses were higher with abatacept 125 mg SC as compared to placebo irrespective of concomitant non-biologic DMARD treatment. Hence the efficacy of the proposed abatacept SC and IV doses appear to have been demonstrated both as monotherapy and in combination with non-biologic DMARDs in patients with active PsA. The US PI states that Orencia can be used with or without non-biological DMARDs and the European SmPC mentions that Orencia can be used alone or in combination with MTX for the treatment of PsA in adult patients.

Safety

The safety profile of abatacept (both SC and IV dosing regimens) in the PsA population appeared comparable with the known safety profile for its other rheumatological indication. No increase in the incidence of malignancies or opportunistic infections was seen in both the PsA studies. Immunogenicity didn't appear to have a relationship with efficacy or safety and appears consistent with the known information from the RA indication. The frequency of AE's was not affected by prior treatment with TNFi or concomitant treatment with MTX or steroids.

Overall conclusion

The Delegate considers the efficacy and safety of abatacept at the dose requested to be satisfactorily established for the new indication for the treatment of active psoriatic arthritis in adults pending further advice from ACM and the PI changes requested herein.

Data deficiencies

The pivotal study included subjects aged 18 years and above. Efficacy and safety of proposed IV dosing with 10 mg/kg was not evaluated in a Phase III study. Evidence for prevention of structural damage by abatacept is limited with no data beyond 1 year.

Summary of issues

The primary issue with this submission is as follows with further information in the Discussion section:

- The Phase IIb study evaluating the efficacy of the proposed IV dosing of abatacept has its limitations and was not supported by a Phase III study. The proposed positive benefit-risk profile for the abatacept IV dosing is based on its comparability with the SC dosing.
- The proposed abatacept IV dosing for PsA in the PI (based on the body weight) is an extrapolation and was not tested in the clinical trials and is proposed by the sponsor to maintain consistency with the RA dosing. This is also the case with the US PI and the European SmPC.

Proposed action

The Delegate had no reason to say, at this time, that the application for Orencia should not be approved for registration, pending further advice from the Advisory Committee on Medicines (ACM).

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACM consider that the efficacy of proposed IV dosing has been adequately established?
2. Does the ACM consider it reasonable to extrapolate the PsA IV dosing to have it consistent with RA IV dosing?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACM Response:

1. The International (foreign) regulatory status included with the recent submission in response to the second round does not match up with the International (foreign) regulatory status provided with the initial submission. Could you please clarify- it appears to an administrative error.
2. Please clarify the mean baseline MTX weekly dose in Study IM101158
3. Please clarify if there were any serious hepatic adverse events in the Phase IIb or Phase III studies.
4. Are there any PsA studies ongoing/planned which are expected to assess the effects of abatacept on long term structural damage?

Response from Sponsor

The sponsor wishes to provide the following comments in support of the use of abatacept in patients with PsA and in the first section address the questions posed to the ACM by the Delegate.

Delegate's questions for ACM

Question 1

> *Issue 1: The Phase IIb study evaluating the efficacy of the proposed IV dosing of abatacept has its limitations and was not supported by a Phase III study. The proposed positive benefit-risk profile for the abatacept IV dosing is based on its comparability with the SC dosing.*
>
> *Question 1: Does the ACM consider that the efficacy of proposed IV dosing has been adequately established?*

Sponsor response

To support this application, the sponsor has provided clinical evidence of efficacy and safety from two well controlled, randomised, double blind, placebo controlled studies (a Phase IIb IV Study IM101158 and a pivotal Phase III SC Study IM101332) in 594 adult patients with active PsA. Both studies demonstrated consistency in efficacy findings for both the IV and SC routes of administration across all clinical outcomes representing the diverse manifestations of PsA. In both studies, the efficacy in arthritis, as assessed by

ACR20 response rate, was supported by benefit in other musculoskeletal endpoints and structural damage. Both the IV and SC administration of abatacept was well tolerated with a safety profile similar to placebo, which was consistent with its use in the treatment of rheumatoid arthritis (RA). In addition, the IV and SC administration of abatacept provided similar abatacept exposures. Population pharmacokinetic analyses were, in general, consistent with the results from previous analyses in rheumatoid arthritis.

The key efficacy results from Studies IM101332 and IM101158 include the following:

Primary endpoint:

- The primary endpoint in both PsA studies was ACR20 response at Day 169.
- Study IM101332 met its primary endpoint, demonstrating that treatment with abatacept 125 mg SC compared with placebo resulted in a statistically significantly higher proportion of subjects achieving an ACR20 response at Day 169.
- Study IM101158 also met its primary endpoint. A higher proportion of subjects achieved an ACR20 response in all 3 abatacept treatment groups compared with placebo at Day 169, with the abatacept 30/10 and 10/10 mg/kg IV groups being statistically superior to placebo. Responses in the 30/10 and 10/10 mg/kg IV groups were similar, suggesting no added benefit of the two loading doses of 30 mg/kg IV.

Other key endpoints:

- A numerically higher proportion of subjects, both among those who were TNFi-naive and who were TNFi exposed, achieved an ACR20 response in the abatacept group compared with the placebo group in the two studies.
- A numerically higher proportion of subjects in the abatacept group, compared with the placebo group, met the criteria for an ACR50 and ACR70 response at Day 169 in both studies. The proportions were higher in the abatacept groups than in the placebo group in both TNFi-naive and TNFi-exposed subjects (in both ACR50 and ACR70 for IM101332 and in ACR50 for IM101158).
- The mean improvement from baseline in the DAS28-CRP score at Day 169 was numerically greater in the abatacept compared with the placebo groups in both studies.
- The proportion of subjects with a HAQ response (decrease from baseline of at least 0.35 for Study IM101332 and of at least 0.30 for Study IM101158) was numerically greater in the abatacept compared with the placebo groups in both studies.
- In both studies, the mean decrease in the HAQ was numerically greater in the abatacept than in the placebo groups at Day 169, with 95% confidence intervals of the difference between abatacept and placebo excluding zero.
- Although difficult to definitively demonstrate in a 6 month placebo controlled trial in PsA, inhibition of structural damage with abatacept at Day 169 was supported by numerically greater improvements in synovitis, oedema, and erosion as assessed by magnetic resonance imaging (MRI) in IM101158 at Day 169, and fewer subjects with radiographic progression of X-rays in Study IM101332 at Day 169 in the abatacept than in the placebo groups.
- There was a numerically greater improvement in enthesitis and dactylitis in the abatacept groups compared with placebo in both studies at Day 169.
- The PASI50, PASI75 responses and target lesion (TL) scores showed a modest improvement in psoriasis in abatacept compared with placebo treated subjects in both studies at Day 169.

- Subjects in the abatacept group reported numerically greater improvements from baseline in the PCS of the SF-36 than subjects in the placebo group in both studies at Day 169.
- During the open label period, efficacy was maintained or improved for the subjects who remained on abatacept, and improved for the subjects who transitioned from placebo to abatacept.

Key safety results from the pivotal Phase III study (Study IM101332) and the Phase IIb study (Study IM101158) support the use of abatacept in subjects with active PsA:

- In the short term period of each study, abatacept (SC or IV) was well tolerated and had a safety profile that was similar to placebo.
- Long-term safety results for abatacept in both studies were consistent with the safety results in the short term period.
- In the pivotal study (Study IM101332), the safety of abatacept treatment was evaluated in the following subgroups and the safety profiles were similar between the subgroups:
  - subjects with or without prior exposure to TNFi agents
  - subjects with or without concomitant MTX treatment

Overall, the safety profile of abatacept in adults with active PsA was consistent with the previous clinical experience of abatacept in adults with RA. There were no new or unexpected safety signals.

Abatacept has also demonstrated clinically relevant efficacy in the articular domain comparable to other recently approved therapies for PsA. Indirect cross-study comparisons of abatacept with other recently approved agents show that comparable efficacy is observed when the ACR20 responses among the TNFi naive subjects from these trials are compared (Tables 39 and 40).

Table 39: ACR 20 Responses for abatacept and recently approved therapies for PsA

Agent	Study	Dose	TNFi-exposed subjects	Agent		Placebo		Effect size (ACR 20 agent - ACR 20 placebo)
				n	ACR 20 (%)	n	ACR 20 (%)	
Abatacept	IM101158	10 mg/kg IV	37%	40	47.5	42	19.0	28.5
	IM101332	125 mg SC	61%	213	39.4	211	22.3	17.1
Apremilast	PALACE-1, 2, 3 pooled*	30 mg BID	22%	497	37.0	496	18.8	18.2
Secukinumab	PsA Study 2 (without IV loading)	150 mg SC	35%	100	51.0	98	15.3	35.7
		300 mg SC	35%	100	54.0	98	15.3	38.7
Ustekinumab	Study 1	45 mg SC	0%	205	42.4	206	22.8	19.6
		90 mg SC	0%	204	49.5	206	22.8	26.7
	Study 2	45 mg SC	58%	103	43.7	104	20.2	23.5
		90 mg SC	58%	105	43.8	104	20.2	23.6

*Week 16 data
n is the number of subjects treated

Table 40: ACR 20 responses for abatacept and recently approved therapies for PsA; TNFi naive subjects

Agent	Target	Study	Dose	Agent		Placebo		Effect size (ACR 20 agent - ACR 20 placebo)
				n	ACR 20 (%)	n	ACR 20 (%)	
Abatacept	CD80/86	IM101158	10 mg/kg IV	27	55.6	30	20.0	35.6
		IM101332	125 mg SC	84	44	81	22.2	21.8
Certolizumab	TNF	RAPID-PsA	400 mg SC/month	219	60.3	110	26.4	33.9
Apremilast	PDE4	PALACE-1*	30 mg BID	120	43	118	24	19
Secukinumab	IL-17	PsA Study 2	150 mg SC	63	63	63	16	47
		(without IV loading)	300 mg SC	67	58	63	16	42
Ustekinumab	IL-12/23p40	Study 1	45 mg SC	205	42.4	206	22.8	19.6
			90 mg SC	204	49.5	206	22.8	26.7
		Study 2	45 mg SC	43	53.5	42	28.6	24.9
			90 mg SC	47	55.3	42	28.6	26.7

*Week 16 data
n is the number of subjects treated

Although not statistically significant, abatacept treatment resulted in modest improvements across all skin assessments. No new forms of psoriasis developed in response to abatacept treatment in the controlled periods of the two studies. The severity of the psoriasis and the arthritis may be discordant in PsA, and there are patients with moderate or severe arthritis who have well-controlled or no to minimal psoriasis.

A precaution has been included in the PI per the clinical evaluator's request, which was accepted by the Delegate, to limit the use of abatacept to patients for whom additional systemic therapy for psoriatic skin lesions is not required.

In both Studies IM101158 and IM101332, steady-state levels of abatacept were reached by Day 85 and Day 57, respectively. The abatacept IV regimen (weight-tiered 10 mg/kg monthly) and SC dose regimen (125 mg weekly) delivered similar $C_{min,ss}$ concentrations. The exposure-response (E-R) model predicted that $C_{min,ss}$ of abatacept delivered through both dosing regimens is associated with near maximal efficacy for ACR20. This was further confirmed by the clinical efficacy results from Studies IM101158 and IM101332 and exposure-response modelling.

Findings from the Phase IIb Study IM101158 and the pivotal Phase III Study IM101332 were accepted by the Delegate as evidence that satisfactorily establishes the efficacy of abatacept IV and SC in the treatment of PsA patients.

The Delegate also concluded that the study populations included in both studies were representative of the intended target patient population in Australia, and that the design and the efficacy parameters used in Studies IM101158 and IM101332 are broadly consistent with other similar studies and the EU Guideline on treatment of PsA and were considered acceptable.

Key safety results from both studies also support the use of IV and SC abatacept in subjects with active PsA. Abatacept IV or SC was well tolerated and had a safety profile that was similar to placebo during the double blind period. The safety profile of abatacept during the long term open label period was consistent with the double blind period. The safety profile of abatacept in adults with active PsA was consistent with the previous clinical experience of abatacept in adults with RA and there were no new or unexpected safety signals. Abatacept IV and SC had a similar, low rate of immunogenicity in PsA.

Although evidence of efficacy for abatacept IV was only directly established in the Phase IIb study, collectively, the clinical evidence from Studies IM101158 and IM101332 support a favourable benefit-risk profile for both abatacept IV and SC as a therapeutic option for the management of patients with PsA.

Question 2

Issue 2: The proposed abatacept IV dosing for PsA in the PI (based on the body-weight) is an extrapolation and was not tested in the clinical trials and is proposed

by the sponsor to maintain consistency with the RA dosing. This is also the case with the US PI and the European SmPC.

Question 2: Does the ACM consider it reasonable to extrapolate the PsA IV dosing to have it consistent with RA IV dosing?

Sponsor response

The Delegate's Request for ACM Advice states that '*the proposed abatacept IV dosing for PsA in the PI (based on body-weight) is an extrapolation and was not tested in the clinical trials and has been proposed by the sponsor to maintain consistency with the RA IV dosing*'. The sponsor would like to clarify that the IV dose was in fact studied in the clinical trial for PsA.

In Study IM101158, the primary objective was to compare the efficacy of three IV dosing regimens of abatacept versus placebo in a 6 month double blind study of psoriatic arthritis, as measured by the proportion of subjects achieving an ACR20 response at Day 169.[27] The strategy of bridging from RA to PsA was applied to the selection of doses to be studied in the Phase II and Phase III PsA studies, which was based on the clinical experience in RA given the similarities between the two disease states in joints. In RA, the dose range of 0.5 mg/kg to 10 mg/kg showed a rise in efficacy with increasing dose. The exposure-response relationship in RA suggested that the abatacept $C_{min,ss}$ of 10 µg/mL and higher were associated with near maximal efficacy in terms of the probability of achieving ACR20 and maximal reduction in DAS28-CRP. Therefore, a range of doses was selected to evaluate the dose-response relationship of abatacept in PsA, that is, three IV dose regimens (administered on Days 1, 15, 29, and every 4 weeks afterwards) were studied in the Phase II study in PsA (Study IM101158): 3 mg/kg, approximately 10 mg/kg, and 30 mg/kg for two doses followed by approximately 10 mg/kg (30/10 mg/kg). Among the three dosing regimens tested, two were weight-based and one was weight-tiered as shown below.

- 3 mg/kg (calculated dose using subject's body weight at screening).
- 10 mg/kg (weight-tiered dose based on subject's body weight at screening: 500 mg for subjects weighing < 60 kg, 750 mg for subjects weighing 60 to 100 kg and 1 gram for subjects weighing > 100 kg).
- 30 mg/kg (calculated dose using subject's body weight at screening) on Days 1 and 15, followed by 10 mg/kg (weight-tiered dose, based on subject's body weight at screening: 500 mg for subjects weighing < 60 kg, 750 mg for subjects weighing 60 to 100 kg and 1 gram for subjects weighing > 100 kg) thereafter.

The data from Study IM101158 showed that near maximal efficacy in terms of ACR20 was achieved with the 10 mg/kg weight-tiered monthly regimen, resulting in the 10 mg/kg weight-tiered monthly regimen being the recommended dose for PsA patients in the proposed PI. The proposed weight-tiered 10 mg/kg dose for PsA was not an extrapolation from the RA IV dosing, since the proposed weight-tiered 10 mg/kg dose was studied in the clinical trial (Study IM101158).

Clinical relevance and management of patients: Treatment guidelines developed by EULAR and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have identified a need for more aggressive therapy depending on the number of adverse prognostic factors for joint disease in patients with PsA.[24,28], Of the patients treated with the currently approved therapies, 40% to 60% do not achieve ACR20, and the proportion

[27] Study IM101158 short term + long term Clinical Study Report.
[28] Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75:499–510

of subjects achieving an ACR20 is lower for TNFi exposed than in TNFi naive subjects[6,8,9,7,29,10,11,30,12].

Within clinical practice, there remains a need for therapies in PsA that offer a novel mechanism of action and can provide significant improvement in arthritis with an acceptable risk-benefit profile. The need for additional therapies is particularly relevant for those patients who have failed to respond to a TNFi. The data presented in the two studies support the use of abatacept after failure of a TNFi in patients with PsA.

Whilst a number of other therapeutic options are available to rheumatologists for the treatment of PsA, cross-study comparisons are difficult to make due to differences in study design, target populations, geographic differences, and analysis methods used in published results. Indirect cross-study comparisons of abatacept with other recently approved agents support comparable efficacy when applied to a similar population (Table 40).

The availability of both IV and SC presentations of abatacept have several advantages. The SC presentation allows for self-administration by patients and can provide greater flexibility, convenience and better adherence. However, some patients prefer not to self-inject, and the IV route of administration can ensure improved compliance and appropriate dosing.

Based on the results of Studies IM101158 and IM101332, abatacept IV and SC has demonstrated efficacy in PsA with a favourable risk-benefit profile. Abatacept is an option for rheumatologists treating PsA patients not requiring systemic therapy for psoriatic skin lesions. It represents an additional therapeutic option for patients with PsA, which offers a novel mechanism of action in this disease.

Delegate's questions for the sponsor

Question 1

Clarification of international (foreign) regulatory status

Sponsor response

The sponsor provided an update on the international regulatory status.

Question 2

Please clarify the mean baseline MTX weekly dose in Study IM101158

Sponsor response

The mean baseline MTX dose ranged between 17.0 and 20.1 mg in the 4 dose groups, and was 18.0 mg in the overall population. It should be noted that subjects who previously had been treated with MTX (prior MTX) and were still treated with MTX at baseline, equals the total population that were treated with MTX at baseline.

Question 3

Please clarify if there were any serious hepatic adverse events in the Phase IIb or Phase III studies.

Sponsor response

In the Phase IIb Study IM101158, there were no hepatic SAEs. In the Phase III Study IM101332, as of the database lock for the 1 year endpoint, there were 2 subjects who experienced serious adverse events of acute cholecystitis and 1 subject who experienced a serious adverse event of biliary dilatation, all while on abatacept treatment.

[29] Mease P. Adalimumab in the treatment of arthritis. Therapeutics and Clinical Risk Assessment 2007;3:133-148

[30] Antoni C, Krueger G, Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64:1150-1157

The second year of the study is ongoing, with open-label abatacept treatment and collection of safety data only (no efficacy data are collected). This data have not been locked and the process of data verification is still ongoing. Since the 1 year database lock, 2 additional SAEs of acute cholecystitis, one serious adverse event of increased ALT and one SAE of 'chronic liver disease with mild activity' were reported.

None of these events from Study IM101332 were considered related to study therapy except for the SAE of increased ALT, which led to discontinuation from study therapy.

Question 4

> *Are there any PsA studies ongoing/planned which are expected to assess the effects of abatacept on long term structural damage?*

Sponsor response

There are no additional sponsored ongoing or planned PsA studies that assess the effects of abatacept on long-term structural damage.

Product information (PI)

The sponsor can confirm that all comments raised on the PI have been addressed.

Risk management plan

In Australia, Orencia has been registered since 2007 (IV) and 2012 (SC) and Pharmaceutical Benefit Scheme (PBS) listed since 2008 (IV) and 2012 (SC) for the treatment of patients with RA, at a dose which is the same as that proposed for use in patients with PsA. There is a well-established Risk Management Plan for the proposed IV and SC dosing, and the sponsor acknowledges the Delegate's conclusion that the RMP and associated assurances are acceptable.

Conclusion

Abatacept provides physicians with the option of treating patients with abatacept after failure of a non-biologic DMARD prior to treatment with other DMARD/biologic therapies with different or less established safety profiles.

Advisory Committee Considerations[31]

The ACM taking into account the submitted evidence of efficacy, and safety, agreed with the Delegate and considered Orencia abatacept (rch) 250 mg powder for IV infusion vial; 125 mg single dose syringe for subcutaneous injection and 125 mg in Single dose ClickJect prefilled autoinjector to have an overall positive benefit-risk profile for the indication;

> *Orencia is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs.*

The product is currently registered for the indication:

[31] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

> *Orencia in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have had an insufficient response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumour necrosis factor (TNF) blocking agents. A reduction in the progression of joint damage and improvement in physical function have been demonstrated during combination treatment with Orencia and methotrexate.*
>
> *Orencia in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.*
>
> *Orencia is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Orencia may be used as monotherapy or concomitantly with methotrexate (MTX). (There is no clinical trial data for the use of Orencia subcutaneous formulation in children, therefore its use in children cannot be recommended.)*

In making this recommendation the ACM

- Noted that the response rate to abatacept in the clinical trial for PsA is consistent with that seen in trials for RA.
- Was of the view that comparability had been demonstrated between the SC and IV dose forms, and therefore the extrapolation of the data from the SC dose form to the IV form is acceptable.
- was of the view that the lack of a Phase III data using the intravenous (IV) dosage form in PsA was not grounds for concern as the comparability of the response seen in the Phase IIb study using the IV form to the response to the subcutaneous (SC) form (in the Phase III study) was seen to be sufficient supportive evidence for this indication and that this is similar to the findings in rheumatoid arthritis for these dose forms.

Specific Advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

Issue 1

> *Does the ACM consider that the efficacy of proposed IV dosing has been adequately established?*

The committee was of the view that, although the data for the proposed IV dosing of abatacept for PsA was limited it was acceptable.

Issue 2

> *Does the ACM consider it reasonable to extrapolate the PsA IV dosing to have it consistent with RA IV dosing?*

The committee considered it acceptable to use the IV dosing regimen described for rheumatoid arthritis for PsA.

Outcome

The registration of Orencia containing abatacept (rch) is approved for the new indication:

> *Orencia is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD)*

therapy has been inadequate. Orencia can be used with or without non-biologic DMARDs.

Specific conditions of registration applying to these goods

The abatacept EU-Risk Management Plan (EU-RMP), version 23.0, date 11 May 2017, DLP 30 June 2016) with Australian Specific Annex (version 9, date 19 September 2017) included with submission PM-2016-03491-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Orencia approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi> .

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