22 June 2017
EMA/455579/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orencia

International non-proprietary name: abatacept

Procedure No. EMEA/H/C/000701/II/0105

Note

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

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List of abbreviations

ABA	Abatacept
ACR	American College of Rheumatology
ACR 20	20% ACR response
ACR 50	50% ACR response
ACR 70	70% ACR response
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMS	Bristol Myers-Squibb
BSA	Body Surface Area
BUN	Blood urea nitrogen
CASPAR	Classification Criteria for Psoriatic Arthritis
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
Cmin	minimum (trough) concentration of drug substance in serum
CPDAI	Composite Psoriatic Disease Activity Index
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
CTLA4	Cytotoxic t-cell lymphocyte-associated protein 4
CV	Coefficient of variation
DAS	Disease Activity Score
DI	Disability Index
DLQI	Dermatology Life Quality Index
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic Acid
ECL	Electrochemiluminescence assay
EIA	Enzyme immunoassay
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue Subscale
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HAQ	Health Assessment Questionnaire
HAQ-DI	HAQ-Disability Index
HDL	High density lipoprotein
hsCRP	High sensitivity CRP
IA	Intra-articular
IEC	Independent Ethics Committee
IM	Intra-muscular
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
IVRS	Interactive Voice Response System
JSN	Joint Space Narrowing
LDAS	Leeds Depression and Anxiety Scale
LDI	Leeds Dactylitis Index
LDL	Low density lipoproteins
LEI	Leeds Enthesitis Index
LT	Long-term
MA	Marked abnormality
MCS	Mental Component Summary
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
N/A	Not available/not applicable
Nail VAS	Physician Global Assessment of Nail Activity
NRI	Non-responder Imputation

NSAID	Non-Steroidal Anti-Inflammatory Drug
OL	Open-label
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PD	Pharmacodynamics
PDE4	Phosphodiesterase 4
PK	Pharmacokinetics
PLA	Placebo
PPD	Purified protein derivative
PPK	Population PK
PsA	Psoriatic arthritis
PsO	Psoriasis
PT	Preferred Term
p-y	Person-year
RA	Rheumatoid Arthritis
RNA	Ribonucleic Acid
ROW	Rest of the World
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SDC	Standard deviation of the paired differences of changes from baseline in total SHS
SE	Standard error
SF-36	Short Form 36 (physical and mental function assessment)
SHS	Sharp/van der Heidje Score
SOC	System Organ Class
ST	Short-term
TAO	Trial Access Online (eCSR)
TB	Tuberculosis
TL	Target Lesion
TNFi	Tumor necrosis factor-α inhibitor
US	United States
VAS	Visual Analog Scale
VDH	van der Heijde
VLDL	Very low density lipoproteins
WBC	White Blood Count
WOCBP	Women of Child Bearing Potential

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 12 October 2016 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of psoriatic arthritis in adults; as a consequence sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are proposed to be updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. A revised RMP was included in this submission (version 21).

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0128/2014 and P/100/2009 on the agreement of the paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

CHMP Scientific Advice was sought in 2012. The Scientific Advice included questions related to the clinical development of abatacept in psoriatic arthritis. The design of the pivotal Study IM101332 was discussed and agreed upon.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Agnes Gyurasics

Timetable	Actual dates
Submission date	12 October 2016
Start of procedure:	29 October 2016
CHMP Co-Rapporteur Assessment Report	23 December 2016
CHMP Rapporteur Assessment Report	22 December 2016
PRAC Rapporteur Assessment Report	2 January 2017
Updated PRAC Rapporteur Assessment Report	5 January 2017
PRAC Outcome	12 January 2017
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 January 2017
Request for supplementary information (RSI)	26 January 2017
CHMP Rapporteur Assessment Report	23 May 2017
PRAC Rapporteur Assessment Report	23 May 2017
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	9 June 2017
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	15 June 2017
Opinion	22 June 2017

2. Scientific discussion

2.1. Introduction

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.

Abatacept administered intravenously (IV) or subcutaneously (SC), in combination with methotrexate, is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor the treatment of rheumatoid arthritis (RA) in adults. It is also approved for the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with methotrexate. Abatacept IV, in combination with methotrexate, is also indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor.

Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in up to one-third of patients with psoriasis and is usually diagnosed years after the appearance of psoriatic skin disease. TNFi agents were the first biologic agents approved for the treatment of PsA. Ustekinumab, an inhibitor of IL-12/23, apremilast, an inhibitor of PDE4, and secukinumab, an antibody directed against IL-17, were also recently approved for PsA. These 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 (ie, ACR 20) based on clinical trial data. In addition, TNFi-exposed patients may be more resistant to treatment, as the proportion of subjects achieving an ACR 20 was lower for TNFi-exposed than in TNFi-naive subjects in trials of ustekinumab, apremilast, and secukinumab.

This variation was submitted to extend the use of Orencia 250 mg powder for concentrate for solution for infusion (Orencia IV) and for Orencia 125 mg solution for injection (Orencia SC) in the treatment of psoriatic arthritis (PsA).

The following indication was applied for:

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.

Following assessment of the data, the adopted indication is:

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.

The posology is:

ORENCIA 250 mg powder for concentrate for solution for infusion: *To be administered as a 30-minute intravenous infusion at the dose specified in Table 1. Following the initial administration, ORENCIA should be given 2 and 4 weeks after the first infusion, then every 4 weeks thereafter.*

ORENCIA 125 mg solution for injection in pre-filled syringe / pen: *ORENCIA should be administered weekly at a dose of 125 mg by subcutaneous (SC) injection without the need for an intravenous (IV) loading dose.*

The application is based on data from a supportive Phase 2b study with abatacept administered IV (IM101158) and a pivotal Phase 3 study with abatacept administered SC (IM101332). In both studies abatacept was compared to placebo in a 6-month, double-blind, short-term period, followed by an open-label long-term period. The long-term period of Study IM101332 is ongoing.

Scientific Advice was sought in 2012. The design of the pivotal Study IM101332 in psoriatic arthritis was discussed, in particular the lack of active control and the inclusion of both DMARD-IR and TNFi-IR patients in one trial. The current design was found acceptable provided that the study is fully powered for each stratum of patients.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 - Summary of studies contributing to the clinical pharmacology of abatacept in PsA

Study no and phase	Study design/control type	Dose, route and regimen	Duration of study	No of subjects enrolled	The studied PK parameters
IM101158 Phase II	Multinational, multi-center, double-blind, multiple dose level, placebo-controlled study, with the primary efficacy endpoint at day 169. The study was extended for patients who completed the short-term (ST) period, with all patients receiving open-label (OL) abatacept	Dose: ST period; 30/10 mg/kg, 10/10 mg/kg, 3/3 mg/kg or placebo i.v. on days 1, 15,29 and every 28 days thereafter up to day 169. Long-term (LT) period: OL treatment with abatacept ar 10 mg/kg until end of study.	169 days ST; LT until end of study	170 ST/147 LTE	C_{min}
IM101332 Phase III	Multinational, multicentre, double-blind, multiple dose level, placebo-controlled study, with the primary endpoint at day 169. On day 113, patients who had not achieved a ≥ 20% improvement from baseline (day 1) in their swollen and tender join counts were considered treatment failures, removed from their blinded treatment arm, and transitioned to the early escape arm in which they received OL weekly s.c. abatacept 125 mg. *At 1 year, all subjects had the option of entering a 1 year LTE for the collection of safety data only*	Dose: 125 mg weekly s.c. abatacept or placebo Early escape arm: OL treatment with abatacept at 125 mg until end of study. LTE period: OL treatment with abatacept at 125 mg until end of study.	169 days ST (113 days if early escape), 197 days OL, 365 days LTE	424 ST/382 OL/228 LTE	C_{min}

Table 2 - Clinical Studies in Subjects with Psoriatic Arthritis

Study No. Phase/ Status	Countries	Study Population	Study Design	No. Subjects Treated Regimen
IM101332 Phase 3/ ongoing	US, Canada, Mexico, Brazil, Columbia, Chile, Argentina, Peru, Israel, Germany, Poland, Czech Republic, France, Spain, South Africa, Greece, Italy	Adults who met CASPAR criteria, with active disease (≥ 3 tender and ≥ 3 swollen joints) and ≥ 1 psoriatic skin lesion ≥ 2 cm	6-month double-blind, placebo-controlled ST period	213 abatacept 125 mg SC qw 211 placebo SC qw
			6-month OL + 12-month LT extension	382 abatacept 125 mg SC qw (OL Year 1)
IM101158 Phase 2b/ Completed	US, Canada, Germany, France, Italy, Belgium, Spain, The Netherlands, Norway, Australia, Argentina, South Africa	Adults who met CASPAR criteria, with active disease (≥ 3 tender and ≥ 3 swollen joints), and ≥ 1 psoriatic skin lesion ≥ 2 cm	6-month double-blind, multiple-dose, placebo-controlled ST period	Dosing on Days 1, 15, 29 and then every 28 days 43 abatacept 30/10 mg/kg IV 40 abatacept 10/10 mg/kg IV 45 abatacept 3/3 mg/kg IV 42 placebo IV
			≥18-month OL LT period	147 abatacept 10 mg/kg IV every 28 days

Abbreviations: CASPAR: Classification Criteria for Psoriatic Arthritis, IV - intravenous, LT - long-term, OL - open-label, qw - weekly, SC - subcutaneous, ST - short-term, US - United States
Source: Protocols for IM101332 and IM101158

2.3.2. Pharmacokinetics

Data on two clinical studies including also pharmacokinetic (PK) data have been submitted to support the current application (see Table 1 and Table 2). In addition to the clinical study PK data, a PK analysis has been conducted to characterize the abatacept serum concentration-time profile in patients with PsA using a PPK model (based on clinical data from studies IM101158 and IM101332) previously developed with data from patients with RA and individual abatacept exposures estimated by the PPK analysis were used to characterize E-R relationships with respect to the key efficacy endpoints (i.e. ACR, PASI, DAS28) and graphical analyses of safety endpoints (e.g. occurrence of infections and serious infections). The formulation used in the PsA clinical studies has been the same as in the approved i.v. and s.c. formulations for RA.

The immunogenicity of abatacept and the effect of immunogenicity on PK are described in more detail in the Clinical Safety section (and under PK/PD modelling).

Bioanalytical methods

Quantitation of Abatacept in Human Serum

An ELISA assay is used to quantitate abatacept in human serum samples. In the assay, a monoclonal anti-CTLA4 antibody (clone 7F8) is used to capture abatacept from the serum samples. The captured abatacept is detected using a biotinylated monoclonal mouse anti-human CTLA4 antibody (clone 11D4) followed by streptavidin-horseradish peroxidase and a TMB (3,3',5,5'-Tetramethylbenzidine) substrate. The optical densities are read at 450 nm and 620 nm using a microplate reader. Critical reagents include the capture antibody (clone 7F8) and the biotinylated monoclonal mouse anti-human CTLA4 antibody.

The validated linear assay range was 1.0 - 30.0 ng/mL, and within this range the linear correlation coefficient was R2 ≥ 0.985, accuracy %AR ± 20.0 % and precision % CV ≤20.0 %. Assay acceptance criteria also included accuracy requirements for the quality controls.

Table 3 - Bioanalytical methods validation summary for abatacept quantitation

Validated Method	TLIAM-0116
Matrix	Human Serum
Analyte	Abatacept
Capture	Anti-CTLA4 monoclonal antibody, clone 7F8
Detector	biotinylated monoclonal mouse anti-human CTLA4 antibody (clone 11D4)
Regression Model, Weighting:	Logistic Auto Estimate (4-parameter, 1/Y)
Standard Curve	
LLOQ	1.0 ng/mL
ULOQ	30 ng/mL
QC Precision (% CV)	
Intra Assay	≤14.90%
Inter Assay	≤10.97%
QC Accuracy (% Deviation)	Within ±17.98%
Stability	
RT	5 Days
4°C	5 Days
-20°C	6.5 Months
-70°C or -80°C	9.75 Years
Freeze-Thaw	10 cycles

Source: Tandem Validation TNJS08-355A[14,15,16]

Abbreviations: TLIAM - Tandem Labs Immunoanalytical Method, LLOQ - Lower limit of quantification, QC - quality control, RT - room temperature, ULOQ - Upper limit of quantification.

Table 4 – In-study assay performance summary

Clinical Study	Assay Method	Number of Runs	Accuracy (% Bias)[a] for Assay QCs	Precision (% CV)[b] for Assay QCs
IM101158	ELISA, TLIAM-0116	98	-10.3 to 1.2	2.7 to 9.7
IM101332	ELISA, TLIAM-0116	114	-4 to 9.6	1.5 to 8.5

[a] Accuracy acceptance criteria: ± 20% of nominal

[b] Precision acceptance criteria: < 20%

Source: Refer to Table 6 of abatacept bioanalytical study report (BSR) for IM101158[17,18,19] and IM101332[20]

Detection of Anti-Abatacept Antibodies in Human Serum using an ECL method

Antibodies against Abatacept, a CTLA4Ig fusion protein, are measured in human serum from Rheumatoid Arthritis (RA) subjects using an electrochemiluminescent (ECL) immunoassay method utilizing MSD technology, which employs a ruthenium metal chelate (SulfoTag) as the ECL label. The low positive quality control (prepared at 10X in 100% serum), negative control, buffer control, and samples are

diluted 1:2.5 (resulting in a 40% serum solution) and loaded into the appropriate wells of a polypropylene plate. The samples are then acidified, incubated for one hour, and neutralized (20% serum concentration). Finally, an equal volume of 2X label master mix (containing Abatacept-SulfoTag and Abatacept-Biotin buffer) is added (resulting in 10% serum concentration). Samples are incubated on the transfer plate for 2 hours. During this time, anti-Abatacept antibodies will bind to both the Abatacept-SulfoTag and Abatacept-Biotin molecules to form an antibody complex bridge. Samples are then dispensed from the transfer plate onto a Streptavidin -coated MSD assay plate (that has been blocked) and incubated for 1 hour. The Abatacept-Biotin in the complex will bind to the Streptavidin in the wells, allowing unbound material to be washed away. Only the samples that contain antibody bound to both the Abatacept-SulfoTag and the Abatacept-Biotin will generate an ECL signal when a tripropylamine (TPA)-containing read buffer is added to the plate. In the presence of TPA, ruthenium produces a chemiluminescent signal that is triggered when voltage is applied. The signal produced is proportional to the amount of anti-Abatacept antibody present.

The ECL immunoassay utilizing Mesoscale Discovery (MSD) technology was validated at ICON Laboratory Services, Inc., Whitesboro, NY, USA (M08.MSDAnti-Abatacept.huse.4). In this validation, the determination of seropositivity is based on a statistically defined cut point value of the relative reactivity of individual donor serum samples. Anti-abatacept-specific antibodies generated in cynomolgus monkey were affinity-purified for use as positive control. Initial validation was conducted with RA donor serum. The method was cross- validated for PsA, Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN), Inflammatory Bowel Disease (IBD – combined ulcerative colitis (UC) and Crohn's disease), Juvenile Idiopathic Arthritis - Juvenile Rheumatoid Arthritis (JIA/JRA), and pediatric serum to establish screening, confirmatory and titration cutpoints. The ECL assay differentiated between 2 antibody specificities: (1) the 'IgG and/or junction region', and (2) 'CTLA4 and possibly Ig' regions. The assay included a three-tiered testing approach (screen, confirmation, and titer).

Human serum samples with raw responses greater than or equal to the statistically determined cutpoint were tested in the confirmatory assay. A sample was considered seropositive if immunodepletion was observed with abatacept or truncated CTLA4. Confirmed positive samples were titered and reported as positive with a titer value. A sample was considered seropositive if immunodepletion was observed with abatacept or truncated CTLA4 and reported as positive with a titer of $\geq$ 10. The assay sensitivity was estimated during validation as 12.2 ng/mL of antibody in the absence of abatacept. Using the RA cut point, in the presence of 40 µg/mL of abatacept, the assay was able to detect anti-abatacept antibodies at a concentration of 250 ng/mL and in presence of 100 µg/mL of abatacept, the assay was able to detect anti-abatacept antibodies at a concentration of 2000 ng/mL. Confirmed positive samples from Studies IM101158 and IM101332 that were specific for 'CTLA4 and possibly Ig' were characterized for the presence of neutralizing antibodies. The validated assay parameters and assay performance are shown below (Table 5).

Table 5 - Bioanalytical methods for detection of anti-abatacept antibodies

Validated Method	ECL (Method M08.MSDAnti-Abatacept.huse.4)
Species and Matrix	Human Serum
Analyte	Anti-Abatacept antibody
Testing	Screen, Confirm, and Titer
Positive Control	Anti-CTLA4Ig purified monkey antibody
Sensitivity	12.2ng/mL
Drug Tolerance (250 ng/mL Anti-Abatacept Antibody)	Up to 40 µg/mL of Abatacept
Drug Tolerance (2000 ng/mL Anti-Abatacept Antibody)	Up to 100 µg/mL of Abatacept
Screening (SCP) and confirmatory Cut-Point (CCP)	
Rheumatoid Arthritis (RA)	SCP: 3.23 CCP: 70.7% Abatacept; 24.2% CTLA4-T
Psoriatic Arthritis (PsA)	SCP: 1.53 CCP: 51.3% Abatacept; 20.5% CTLA4-T
Systemic Lupus Erythematosus (SLE)	SCP: 1.28 CCP: 22.3% Abatacept; 12.8% CTLA4-T
Lupus Nephritis (LN)	SCP: 1.67 CCP: 63.3% Abatacept; 22.3% CTLA4-T
Inflammatory Bowel Disease (IBD - combined ulcerative colitis (UC) and Crohn's disease)	SCP: 2.97 CCP: 18.4% Abatacept; 15.5% CTLA4-T
Juvenile Idiopathic Arthritis - Juvenile Rheumatoid Arthritis (JIA/JRA)	SCP: 3.45 CCP: 29.3% Abatacept; 11.5% CTLA4-T
Pediatric (IM101301 in-study and JIA population)	SCP: 2.65 CCP: 83.5% Abatacept; 17.1% CTLA4-T

232425 171158, 170230, 174709, 176815

Neutralizing Antibodies to Abatacept

Human serum samples from Studies IM101158 and IM101332 that confirmed positive to abatacept with 'CTLA4 and possibly Ig' specificity and have abatacept serum concentration levels below 1 µg/ml were also characterized for NAb to abatacept using a validated functional cell based bioassay (TLIAM-0004).

In this bioassay, Jurkat T cells transfected with the luciferase gene, under the control of the IL-2 promoter, are costimulated with Daudi B cells in the presence of anti-CD3 antibody. The costimulation activates the IL-2 promoter, which in turn produces luciferase protein. The resulting luminescent signal is measured using a Luciferase Assay System. In this system, abatacept produces a dose-dependent decrease in luciferase activity. In samples containing neutralizing antibody to abatacept, the abatacept activity is mitigated, resulting in increased luciferase activity compared to the pre-dose (Day 1) sample. The bioassay evaluates neutralizing antibody presence by comparing the response of the postdose seropositive serum sample to its corresponding Day 1 (baseline/pre-study) sample. Each post-dose and pre-dose sample was spiked with 3 concentrations of abatacept (0.10, 0.25, and 0.50 µg/mL) and the response values in relative light units (RLUs) were regressed on log of abatacept concentration. A linear-regression function was fit to the spiked response values, separately for each sample and its corresponding Day 1 sample, at abatacept concentrations of 0.10, 0.25, and 0.50 µg/mL. A seropositive sample was considered to have neutralizing antibody presence if either of the following was true:

- The regression lines for the seropositive sample and its corresponding Day 1 were parallel and both the estimated inhibition factor and the lower limit of the 95% CI for the inhibition factor were > 1 (demonstrating an upward shift of the seropositive sample relative to the Day 1 sample).

- The seropositive sample and its corresponding Day 1 regression functions were not parallel and the median predicted concentration of the 3 values at the 0.25 µg/mL abatacept concentration level calculated from the Day 1 regression function for the seropositive sample was < 0.16 µg/mL. This value (0.16 µg/mL) was based on validation experiments and used as the cutoff for identifying significant neutralizing activity when parallelism was not demonstrated.

The assay was validated at Covance (Tandem Labs Inc., Trenton, NJ, US). The assay acceptance criteria included requirements for recovery at the curve midpoint and the difference between the spiked and non-spiked standard. The assay sensitivity was determined as 2.5 µg/mL neutralizing antibody in neat serum and drug interference was observed above the level of 1 µg/mL.

Clinical study in PsA patients (IM101158)

This study was the first study of abatacept in PsA patients (a total of 170 patients [both men and women] were randomized and treated; 147 completed the short-term [ST] period) and consisted originally of 2 study periods: a 6-months double-blind, placebo-controlled ST period and an open-label long-term extension (LTE) period for subjects who completed the ST period. The study IM101158 was, however, terminated prematurely by the Bristol-Myers Squibb (BMS; Jan 2011) due to the modest efficacy on skin-related parameters.

The PK of abatacept was a secondary objective and studied by determining the C_{min} concentrations at ST period. The prediction PK of 3 abatacept treatment groups (see below) using population PK methodology was not performed as originally planned (the reason for not using the PPK methodology was that no additional information related to the PK would have been received).

ST-period

The treatment groups were as follows:

- Abatacept 3/3 mg/kg regimen by i.v. infusion: 3 mg/kg (calculated dose using patient's body weight at screening) on days 1, 15, 29, 57, days 85, 113 and 141
- Abatacept 10/10 mg/kg regimen by i.v. infusion: 10 mg/kg (weight–tiered dose based on patient's body weight at screening (i.e. fixed dose): 500 mg for patients < 60 kg, 750 mg for patients weighing 60-100 kg and 1g for patients weighing > 100 kg) on days 1, 15, 29, 57, 85, 113 and 141
- Abatacept 30/10 mg/kg regimen by i.v. infusion: 30 mg/kg (calculated dose using patient's body weight at screening) on days 1 and 15, followed by 10 mg/kg (weight-tiered dose based on patient's body weight at screening: 500 mg for patients < 60 kg, 750 mg for patients weighing 60-100 kg and 1g for patients weighing > 100 kg) on days 29, 57, 85, 113 and 141
- Placebo (dextrose 5% in water) or normal saline by i.v. infusion on days 1, 15, 29, 57, 85, 113 and 141.

Abatacept infusions (approximately 30 minutes) were administered at about the same time of day throughout the duration of the study. The patients were seated when i.v. infusions were administered (unless the clinical situation warranted another position).

Concomitant use of MTX during the study was permitted, provided the subject had been on a stable dose for at least 3 months prior to screening and continued at the stable dose during the study.

In the ST-period, 42 patients were in the abatacept 30/10 mg/kg group (n = 37 completed), 40 patients in the 10/10 mg/kg group (n = 34 completed), 45 patients in the 3/3 mg/kg group (n = 43 completed) and 42 patients in the placebo group (n = 33 completed).

Blood samples (3 to 5 ml/sample) were collected from patients from the arm contralateral to the infusion site just prior to the administration of the i.v. infusion on days 1, 15, 29, 57, 85, 113, 141, and 169 during

the ST period. On days 1, 15, and 85, a blood sample was also collected at about 30 minutes (end of infusion). In addition, a single blood sample was collected at any time between days 92 and 106. For patients who terminated or discontinued from the study early, blood samples were collected 28, 56 and 85 days after the last dose of study drug administration.

The trough plasma concentration (C_{min}) concentrations of abatacept in human serum were assayed using a validated enzyme-linked immunosorbent assay (ELISA) by Tandem Laboratories (West Trenton, New Jersey, US). The sample analyses were performed at Tandem Labs, a LabCorp Company, West Trenton, US (see above for details).

PK analysis set

The PK analysis population included 130 patients who received abatacept and had at least 1 evaluable serum C_{min} concentration.

Analyses of PK

Summary statistics were tabulated for C_{min} of abatacept by study day and treatment group. Geometric means and coefficients of variation were presented for C_{min} concentrations.

PK results

Geometric mean C_{min} of abatacept at steady-state was dose-related during the ST period, when administered as a 30- or 60-minute i.v. infusion on days 1, 15, 29, and every 28 days thereafter to PsA patients (see Table 6).

Table 6 - Summary statistics for abatacept C_{min} concentrations (µg/ml)

Treatment[a] (mg/kg)	Day 15 Cmin (µg/mL)	Day 29 Cmin (µg/mL)	Day 57 Cmin (µg/mL)	Day 85 Cmin (µg/mL)	Day 113 Cmin (µg/mL)	Day 141 Cmin (µg/mL)	Day 169 Cmin (µg/mL)
	GM [N] (%CV)	GM (%CV)	GM (%CV)	GM (%CV)	GM (%CV)	GM (%CV)	GM (%CV)
Aba 3/3	12.8 [43] (53.7)	15.4 [43] (30.0)	9.0 [44] (55.2)	8.2 [41] (37.4)	7.6 [43] (56.6)	6.9 [42] (40.8)	7.8 [42] (56.3)
Aba 10/10	45.1 [38] (37.2)	46.9 [39] (33.7)	23.9 [39] (37.5)	24.4 [35] (40.3)	29.6 [33] (43.1)	23.6 [34] (37.8)	24.3 [34] (40.8)
Aba 30/10	115.3 [43] (29.4)	176.2 [41] (33.4)	53.1 [40] (44.3)	33.1 [37] (49.7)	31.5 [35] (54.9)	25.0 [35] (34.6)	26.6 [36] (39.0)

[a] Abatacept dose was administered on days 1, 15 ± 3, 29 ± 3, 57 ± 7, 85 ± 7, 113 ± 7, 141 ± 7 and 169 ± 7 in the double blind period.

Abbreviations: Aba =Abatacept , GM = Geometric Mean, CV = Coefficient of Variation

The steady-state levels of abatacept were reached by day 57 for the "3/3" mg/kg and "10/10" mg/kg dosing regimen and by day 85 for the "30/10" mg/kg dosing schedule (see Figure 1). Also, the steady-state trough levels of abatacept were similar for the "10/10" mg/kg and the "30/10" mg/kg dosing regimen.

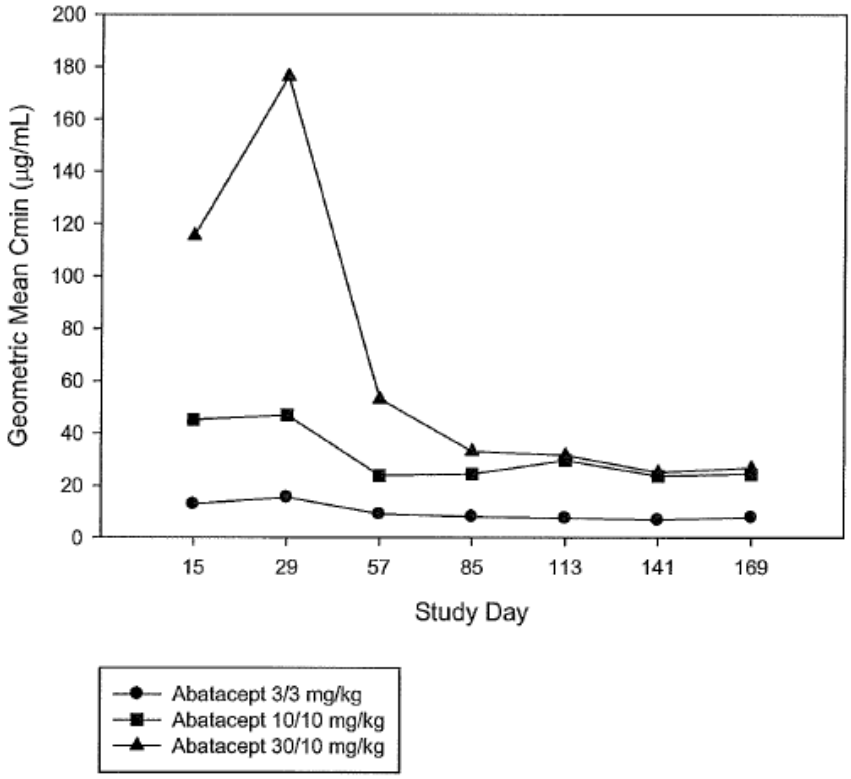


Figure 1 - Geometric mean abatacept C_{min} (µg/ml) versus study day, by dosing schedule.

The trough concentrations over time of the 2 subjects with on-treatment ADA at Day 169 show that concentrations remained consistent before and at the presence of ADA.

Clinical study in PsA patients (IM101332)

The study was first 24 weeks (169 days) as double-blind and thereafter open-label (OL) up to 28 weeks. At the end of the OL period, patients had the option of entering a 1-year LTE period. During the double-blind period, patients received weekly s.c. abatacept 125 mg or placebo. During the OL and LTE period, all patients received weekly abatacept 125 mg s.c.

In the ST period, 424 patients (both men and women, n = 213 in abatacept group [total TNFi-naive n=84 and total TNF-exposed n =129] and n = 211 in the placebo group [total TNF-naïve n =81 and total TNF-exposed n =130]; mean age of 50.4 years) were randomized and received at least 1 dose of double-blind drug.. Overall, 76/213 (35.7%) of subjects in the abatacept group and 89/211 (42.2%) of subjects in the placebo group were designated as Early Escape; these subjects left the double-blind treatment period and transitioned to the OL Period at Day 113. 125 patients in abatacept group and 98 patients in the placebo group completed the full 169 days of the ST period.

Overall, 382 patients entered the OL period (197 had received abatacept and 185 had received placebo in the ST period). The LTE population consisted of 310 patients (153 had received abatacept and 157 had received placebo in the ST period).

The PK of abatacept was as an exploratory objective. In the ST period, serum samples for measure the C_{min} concentrations of abatacept were drawn on pre-dose days 1, 85 and 169 in all patients. Additional a subset of patients also had PK samples drawn on pre-dose days 29, 57, 113, and anytime between days 114 and 120. In the OL period C_{min} concentrations were assessed for LTE day 57 and day 197 outcomes. The objective was to determine PK and exposure-response relationship of s.c. abatacept in PsA patients.

In the PK sub-study for 3 patients PK samples were collected and abatacept serum concentration data reported although the patients were not consented to the PK sub-study. The data were included in the concentration summaries. This protocol deviation was thought to have no effect on the results or conclusions of the study.

Validated ELISA method was used to measure concentrations of abatacept in serum (see above for details).

PK analysis set

ST period

In the full PK analysis set, all patients who received at least one dose of abatacept and who had at least 1 PK result reported after start of the medication were included. The evaluable PK analysis set: this population was a sub-set of the PK analysis population and consisted of the evaluable subjects for PK analysis. For all PK summaries and plots, a patient was evaluable for PK analysis at a specific day if the PK measurements were collected in the 4 to 10 days window after the previous s.c. abatacept dose and prior to the dose of the specific day. The PK analysis set contained 213 PsA patients.

OL and LTE period

Serum concentration data were available for 315 patients at OL period day 57; this included 162 patients who received abatacept and 153 patients who received placebo during the ST period.

Serum concentration data were available for 289 patients at OL period day 197; this included 144 patients who received abatacept and 145 patients who received placebo during the ST period.

PK analysis

The PK parameter C_{min} was summarized by geometric mean and %CV. Data obtained from the current study was combined with the data from other historical abatacept RA and PsA (IV) studies to perform population PK (PPK) analysis.

PK results

ST period

The steady-state in C_{min} concentrations was reached at day 57 (see Table 7). From day 57 and onwards, the steady-state C_{min} concentrations remained consistent over time.

Table 7 - Summary statistics of abatacept C_{min} values (µg/ml) during ST-period (Evaluable PK analysis set)

Treatment	Cmin (µg/ml)					
	Statistics	Day 29	Day 57	Day 85	Day 113	Day 169
Abatacept s.c.	N	120	116	181	132	110
	Mean	22.07	27.93	28.37	29.00	29.74
	SD	11.684	15.132	13.590	13.984	14.184
	Geom. mean	18.37	22.26	24.84	24.84	25.61
	%CV	52.94	54.18	47.90	48.23	47.70
	Median	19.60	25.07	26.97	27.51	28.52
	Min	0	0	1	1	1
	Max	54	85	88	92	82

The abatacept C_{minss} achieved with the 125 mg s.c. weekly regimen was associated with the near maximal efficacy response (ACR20) in PsA patients.

OL and LTE period

The C_{minss} concentrations of abatacept remained consistent over time during the OL period in patients who received abatacept during the ST period and patients who received placebo during the ST period and transitioned to abatacept in the OL period (see Table 8).

Table 8 - Summary statistics of abatacept C_{min} values (µg/ml) during OL period (evaluable PK analysis set)

Treatment#	C_{min} (µg/ml)		
	Statistics	Day 57 OL	Day 97 OL
Abatacept s.c.	N	162	144
	Mean	30.56	29.98
	SD	13.537	13.966
	Geom. mean	27.12	24.53
	%CV	44.29	46.58
	Median	28.16	28.59
	Min	2	0
	Max	80	73
Placebo	N	153	145
	Mean	24.16	28.29
	SD	9.303	10.538
	Geom. mean	22.10	26.09
	%CV	38.51	37.25
	Median	23.82	27.70
	Min	2	5
	Max	54	54

#Treatment groups represent treatment received in the double-blind ST period.

In both ST and OL/LTE periods C_{min} concentrations remained consistent before and after the presence of anti-drug antibodies (ADA). Therefore, the presence of ADA did not appear to consistently affect abatacept C_{min} values.

Absorption

Based on the population PK analysis, the absolute bioavailability of SC abatacept is 77%.

Distribution

Population PK analysis of the RA and PsA combined data did not reveal any difference between the steady-state volume of distributions of the patient groups.

Elimination

Abatacept clearance in patients with PsA was approximately 8% lower relative to patients with RA. This difference was not considered clinically meaningful.

Dose proportionality and time dependencies

No new data have been submitted in this application, which was considered acceptable by the CHMP.

Special populations

No new data have been submitted in this application, which was considered acceptable by the CHMP.

Pharmacokinetic interaction studies

No new data have been submitted in this application, which was considered acceptable by the CHMP.

Pharmacokinetics using human biomaterials

No new data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.3. Pharmacodynamics

Mechanism of action

The mechanism of action of abatacept in PsA is not completely clarified. Abatacept has greater efficacy in the joints vs. skin in PsA and the reason for this is thought to be the distinct pathologies with divergent roles of immune cells in skin versus synovial inflammation in PsA. T cells are thought to have a less important role in skin inflammation than in joint inflammation.

Primary and secondary pharmacology

No new data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.4. PK/PD modelling

PK/PD modelling

The PK of abatacept in patients with RA has been previously characterized by PPK analysis with data from 11 clinical studies (4 Phase 2 and 7 Phase 3) where abatacept was either administered intravenously (IV) or subcutaneously (SC). Abatacept concentration-time data were well characterized by a linear, two-compartment PPK model with zero-order IV infusion, first-order SC absorption, and first-order elimination. Abatacept clearance (CL) increased with body weight (BWT), calculated glomerular filtration rate (CGFR), and swollen joint count (SWOL); decreased with age (AGE), albumin (ALB), and was lower in females and higher in patients on concomitant non-steroidal anti-inflammatory drugs (NSAID). Central and peripheral volume of distribution (VC and VP) increased with BWT and bioavailability for SC formulation (F) was lower for the Phase 2 SC formulation than the Phase 3 SC formulation studied in the RA program.

Previous exposure response (E-R) analyses for efficacy and safety following treatment of abatacept for RA have been conducted. An E-R model was developed for ACR20 response and DAS28-CRP following abatacept IV and SC administration in patients with RA. The probability of ACR20 response was described by a logistic regression model with a hyperbolic logit with respect to steady-state trough concentrations (C_{minss}). A nonlinear mixed-effects inhibitory maximum pharmacologic effect (E_{max}) model with respect to time was developed to characterize the E-R of abatacept exposure and DAS28 up to 6 months after initiation of treatment. Abatacept C_{minss} was the best measure of exposure for predicting DAS28 response with an E_{max} -time course model.

The objectives of the current PK/PD modelling and simulations were:

- To characterize the PK of abatacept following i.v. and s.c. administration in patients with PsA and to determine the effects of disease (PsA versus RA) on abatacept PK parameters and exposure.
- To characterize the relationship between abatacept exposure and efficacy in patients with PsA.
- To graphically explore the relationship between abatacept exposure and safety in patients with PsA.

Population pharmacokinetic (PPK) model

The PPK analysis was conducted to characterize the abatacept serum concentration-time profile in PsA patients using a PPK model previously developed with data from patients with RA.

The PPK model was developed in 4 stages:

1. External validation using the final RA model and data from patients with PsA was performed using a prediction-corrected visual predictive check (pcVPC).
2. A base model was developed by re-estimating the parameters of the previously determined final model for RA using pooled RA and PsA data.
3. A full model was developed to assess the effect of PsA (versus RA) on abatacept clearance (CL).
4. A parsimonious final model was tested by performing backward elimination on disease type (PsA versus RA) using 0.1% level of significance, corresponding to an increase in the objective function of 10.83 for 1 degree of freedom.

Dataset

PPK analysis included the following RA studies: 3 phase 2 i.v. studies (IM103002, IM101100, and IM101101); 1 phase 2 s.c. study (IM101063); 3 phase 3 i.v. studies (IM101102, IM101029, and IM101031); and 4 phase 3 s.c. studies (IM101167, IM101173, IM101174 [IM101174 PK sub study is also included], and IM101185), and following PsA studies: 1 phase 2b i.v. study, IM101158 (double-blinded period), and 1 phase 3 s.c. study, IM101332 (double-blinded and OL periods).

The final PPK analysis dataset had 12962 serum concentration values from 2244 RA and 493 PsA patients who received i.v. infusion and/or s.c. injection of abatacept. Of these, a total of 2580 observations were from PsA patients.

PsA patients were more commonly male (46.7% vs. 19.4%), had higher baseline body weight (86.5 ± 20.0 kg vs. 74.1 ± 19.2 kg), and were more commonly co-medicated with NSAIDs (74.4% vs. 21.7%) but less commonly with methotrexate (63.1% vs. 92.4%) and with corticosteroids (41.8% vs. 67.9%) than RA patients. PsA patients were also more often Caucasian (88.0% vs. 80.1%) and had lower baseline swollen and tender joint count than RA patients. Baseline age, calculated GFR and liver function tests were similar in both patient groups.

Methods

The analyses were performed using NONMEM 7.3.0. The previously developed PPK model was a linear 2-compartment, zero-order IV infusion, first-order SC absorption, and first-order elimination with a combined residual error model, random effects on F, first-order absorption rate constant (KA), CL, VC, inter-compartmental clearance (Q), and VP; and a full block correlation matrix of the random effects of CL, VC, Q, and VP. The following covariates were included: weight (BWT), age (AGE), gender (SEX), co-administration of NSAIDs (NSAID), albumin (ALB), calculated glomerular filtration rate (CGFR), swollen joint count (SWOL), and SC formulation (FORM). The covariate effects on the typical values of structural model parameters are described by the following equations:

$$CL_{TV} = CL_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{CL_{BWT}}\left(\frac{AGE_b}{AGE_{ref}}\right)^{CL_{AGE}}\left(\frac{ALB_b}{ALB_{ref}}\right)^{CL_{ALB}}\left(\frac{CGFR_b}{CGFR_{ref}}\right)^{CL_{CGFR}} \times \left(\frac{SWOL_b+1}{SWOL_{ref}+1}\right)^{CL_{SWOL}} \times exp(SEX \times CL_{SEX} + NSAID \times CL_{NSAID}) \quad \text{Equation 4.1.2.2A}$$

$$VC_{TV} = VC_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VC_{BWT}} \quad \text{Equation 4.1.2.2B}$$

$$Q_{TV} = Q_{TV,ref} \quad \text{Equation 4.1.2.2C}$$

$$VP_{TV} = VP_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VP_{BWT}} \quad \text{Equation 4.1.2.2D}$$

$$F_{TV} = F_{TV,ref} + FORM \times F_{FORM} \quad \text{Equation 4.1.2.2E}$$

where $P_{TV,ref}$ is the typical value at the reference or baseline values for appropriate covariates (BWT_{ref} = 70 kg, AGE_{ref} = 50 yr, ALB_{ref} = 4.0 g/dL, $SWOL_{ref}$ = 16, $CGFR_{ref}$= 90 mL/min/1.73m^2, SEX_{ref}= Male, $NSAID_{ref}$= No, $FORM_{ref}$= Phase 3 formulation).

No single pairing of covariates to be incorporated in the model simultaneously was highly correlated (Pearson correlation coefficients < |0.42|; Spearman rank test correlations < |0.44|).

Bioavailability included in the PPK model is the absolute bioavailability, modelled using the inverse logit function:

$$F_{Absolute} = 1/[1 + exp(-F_{TV} - F_{IIV})] \quad \text{Equation 4.1.2.2F}$$

where $F_{Absolute}$ is the individual absolute bioavailability, F_{TV} is the model estimated typical value for bioavailability prior to transformation, F_{IIV} is the model estimated interindividual variability (IIV) for bioavailability prior to transformation.

To prevent flip-flop of parameter estimates and ensure that rate of absorption was always higher than the rate of elimination, individual KAs were expressed as the sum of the estimated relative rate of absorption and rate of elimination for that individual as shown in the following:

$$KA = KA_{TV} \times exp(KA_{IIV}) + K_{el} \quad \text{Equation 4.1.2.2G}$$

where KA is the individual absolute rate of absorption, KA_{TV} is the model estimated typical value for the relative rate of absorption, KA_{IIV} is the model estimated IIV for relative rate of absorption. K_{el} is the individual rate of elimination, which is the quotient of the individual clearance (CL) and central volume (VC).

The effect of anti-drug antibody (ADA) status on abatacept concentration and CL in PsA patients was explored graphically. Immunogenicity was treated as a stationary categorical covariate (positive/negative).

The focus of the full PPK model was the assessment of the effect of PsA (versus RA) on abatacept CL, after accounting for the effect of covariates from the base model. Due to the sparse sampling design of the PsA studies (mostly through samples), the informational content of the data with respect to most PK parameters was limited. Therefore the estimates of the PK parameters and their covariate effects, with the exception of CL, were anchored by the estimates from the final RA model. The effect of PsA, relative to the PK parameter value for a reference (RA) patient, was given by the following expression:

$$P_{TV,i} = P_{REF}(e^{CL_{PsA}})^{IPsA_i} \qquad \textit{Equation 4.1.2.3A}$$

where P_{REF} is the value of the parameter for the reference patient with RA; CL_{PsA}, is the estimated model parameter for the effect of PsA; and $IPsA_i$ is the indicator variable for PsA status of patient i, respectively (1=yes, and 0=no).

Final PPK model: A continuous covariate was considered clinically relevant if its inclusion resulted in the 95% confidence interval (CI) for lowest and highest values of the covariate exceeding the range of 80%-125% of the typical value of the PK parameter (including all other covariates in the model). For a categorical covariate, clinical relevance was defined as the 95% CI exceeding the range of 80%-125% of the typical value with this covariate. Covariates were considered to not be clinically relevant if the associated change in point estimates was between -20% and +25% and the 95% CI fell within 80%-125% of the reference value.

PPK model application:

The final PPK model was used to obtain maximum a posteriori (MAP) Bayesian estimates of the PK parameters and measures of exposure (C_{min}, C_{max}, Cav, C_{minss}, C_{maxss}, and C_{avss}) for each patient in the PPK analysis dataset. The effect of disease type (PsA or RA) and administration route on abatacept steady-state exposures was performed using graphical assessment.

C_{min} and C_{minss} were defined as the theoretical trough concentration obtained at the time of each DAS28-CRP collection or at steady-state, respectively. C_{max} and C_{maxss} were defined as the maximum concentration at the time of each DAS28-CRP collection or at steady-state, respectively. Using the final PK model, the area under the model-predicted concentration-time curve over the nominal dosing interval was obtained using integration in NONMEM. C_{max} was identified from the model-predicted concentration-time curve over the nominal dosing interval for each patient. C_{avg} was calculated by dividing the area under the concentration-time curve between visits with collection of DAS28-CRP by nominal dosing interval, for example 14 days for every 2 weeks (Q2W). C_{avgss} was calculated by dividing the area under the steady-state concentration-time curve (AUS_{ss}) between visits with collection of DAS28-CRP by nominal dosing interval, for example 14 days for every 2 weeks (Q2W). The applicable AUC_{ss} of each patient was obtained for the purpose of computing C_{avgss} by dividing the abatacept dose by the MAP Bayesian estimate of CL.

Stochastic simulations (that is, including inter individual variability based on the final population PK and E-R models) were performed to determine the expected range of abatacept exposures and PD responses in PsA patients. The following dosing regimens were used: low dose [50 mg SC weekly and/or 3 mg/kg IV monthly], 10 mg/kg IV monthly, and 125 mg SC weekly for 6 months of treatment. To conduct these simulations, the efficacy dataset was resampled using covariate information from patients included in the Phase 2b/3 dataset of PsA patients (approximately 564 patients) to generate a dataset of 2000 virtual patients. Dosing, PK, and PK/PD sampling (sampling on Day 169 [Month 6]) were assigned to each virtual patient based on the scenarios described above. Stochastic simulations of the final PK and PK/PD models were then used to obtain the predicted PK and PK/PD outcomes.

Results

Graphical Analysis of ADA in PsA patients

Abatacept concentration values were similar for both ADA negative and positive status (Figure 2). In addition, there appeared to be no obvious trend in the difference in clearance when stratified by ADA status (Figure 3). These results suggest that ADA had little to no impact on the concentration data or PK of abatacept. Therefore, immunogenicity was not formally tested as a covariate in the model.

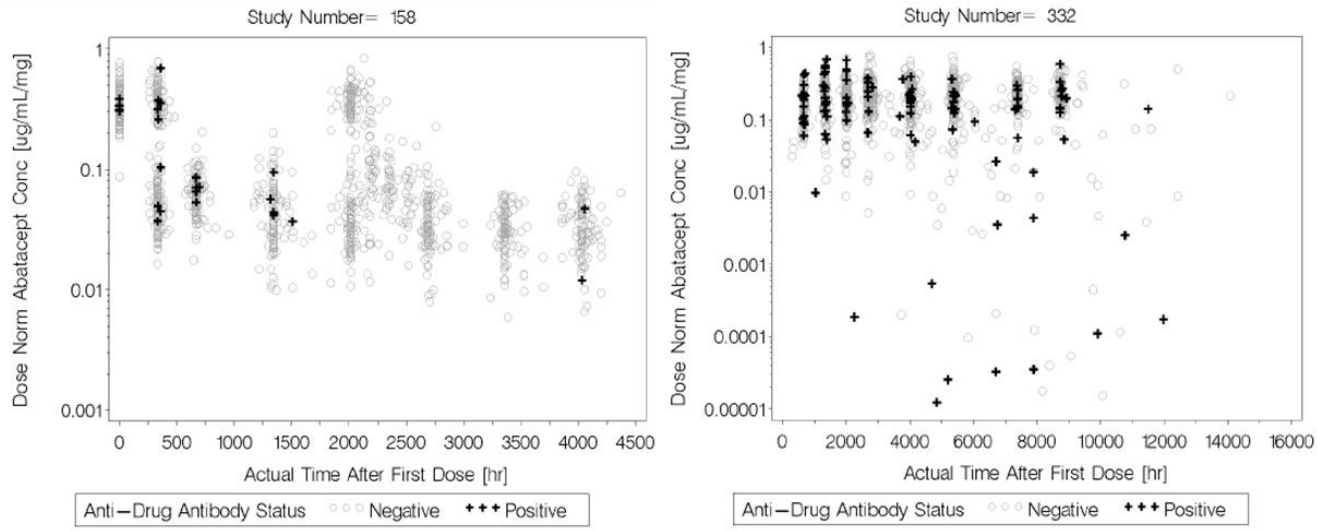


Figure 2 - Dose-Normalized Abatacept Concentration Time Data for PsA Studies, Stratified by ADA Status

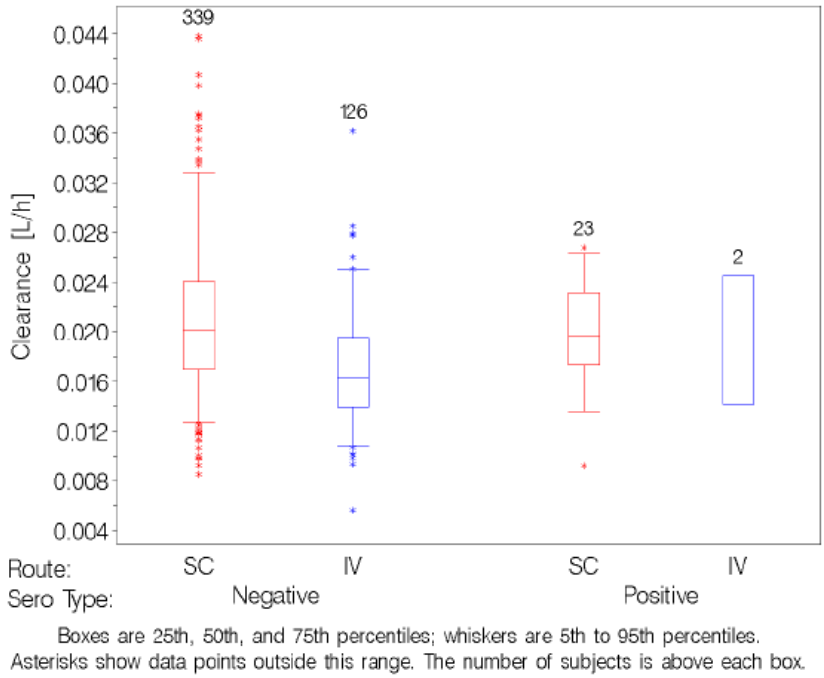


Figure 3 - Effect of Impact of Immunogenicity on Abatacept clearance in PsA Patients, stratified by Route

Base PPK model

Based on the results from the external pcVPC (Figure 4), the previous final RA PPK model adequately described the data from patients with PsA. Therefore, the base PPK model was assumed to be identical to the previously developed final PPK model describing abatacept PK in RA patients; see above for description of the model.

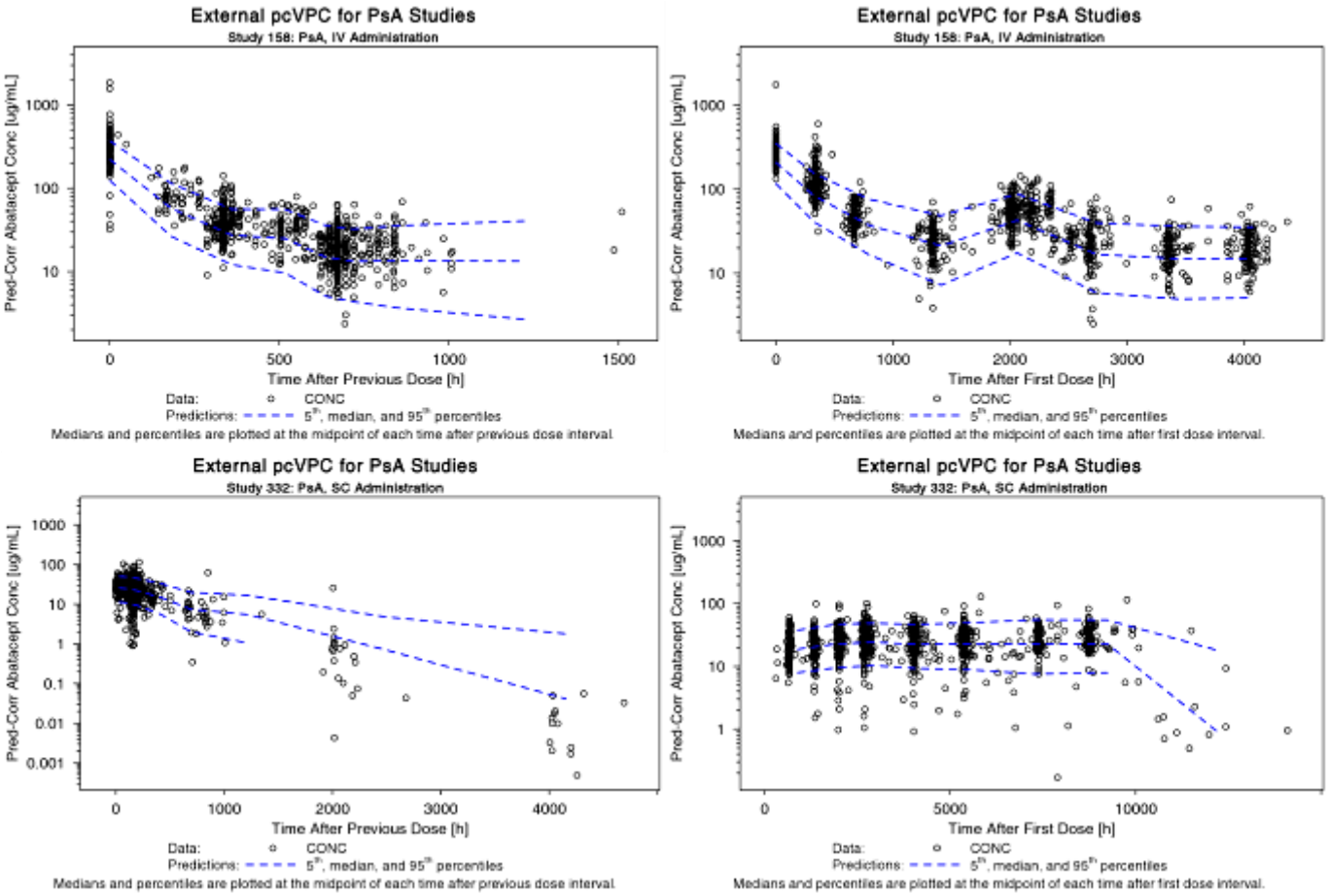


Figure 4 - External pcVPC of Concentration vs. Time After Previous Dose (left) and Concentration vs. Time After First Dose (right), by PsA Study

The parameters of the base PPK model were re-estimated with the inclusion of data from PsA patients (Studies IM101158 and IM101332). In general, parameter estimates were consistent with those of the model in patients with RA; typical values of CL, VC, Q, and VP were changed by <10%. The relative standard errors of the parameter estimates were reasonable with the condition number of the model equal to 190, indicating that the model was stable and not overparameterized. The ETA distributions were approximately symmetrical and the CWRESI plots showed no obvious trend or bias in the predictions for either IV or SC dosing. There was a good agreement between the observed and model-predicted (PRED and IPRED) abatacept serum concentrations greater than 1 µg/mL. Although the model tended to slightly overpredict abatacept concentrations below 1 µg/mL, this is not expected to adversely affect the applicability of the model given the small magnitude of the overprediction, and the small fraction of patients that are expected to have C_{min} below 1 µg/mL for therapeutically relevant abatacept dosage regimens.

The base model was additionally tested by removal of potential outliers identified on the basis of the CWRESI, whereby predicted concentrations associated with |CWRESI| > 6 were considered outliers. When such points were excluded, the differences in base model fixed effect parameters were < 10% as compared to those obtained with these potential outliers included and therefore the points were retained in the model.

Full PPK Model and Final PPK model

The effect of disease type (PsA versus RA) on CL was incorporated into the full model using the Equation 4.1.2.3A (see section Methods above) and resulted in an 8% decrease in clearance for PsA patients. Parameters were estimated with good precision (Table 9). The condition number of the model was 206, indicating that the model was stable and not over parameterized. ETA shrinkage was moderate for CL (19.6%) but high for other parameters (48.9%-83%).

Table 9 - Parameter Estimates of the Full PPK Model

	Final Parameter Estimate		Interindividual Variability / Residual Variability[a]	
Parameter	**Estimate**	**%RSE**	**Estimate**	**%RSE**
CL:Clearance [L/h][b]	0.020	2.4	0.094	6.2
CL:Power of BWT on CL [-][c]	0.65	4.5		
CL:Power Effect of CGFR on CL [-][c]	0.15	16		
CL:Exponential Effect of SEX on CL [-][c]	-0.057	25		
CL:Power Effect of ALB on CL [-][c]	-0.67	12		
CL:Exponential Effect of NSAID on CL [-][c]	0.057	25		
CL:Exponential Effect of SWOL on CL [-][c]	0.080	13		
CL:Power Effect of AGE on CL [-][c]	-0.18	14		
CL: Exponential Effect of DISEASE on CL [-][c]	-0.080	25		
VC:Central Volume [L][b]	3.2	1.5	0.067	16
VC:Power Effect of BWT on VC [-][c]	0.44	12		
Q:Intercompartmental CL [L/h]	0.025	13	0.430	33
VP:Peripheral Volume [L][b]	4.0	5.3	0.360	16
VP:Power Effect of BWT on VP [-][c]	0.48	17		
KA: Absorption Rate Constant [1/h]	0.0025	27	1.90	42
F1:Bioavailability of SC formulation [-][b,d]	1.3	9.4	0.630	17
F1:Additive Effect of Phase 2 SC Formulation on F1 [-][c]	-1.1	14		
cov(IIV in VC, IIV in CL)[e]	NA	NA	0.044	21
cov(IIV in Q, IIV in CL)[e]			0.092	31
cov(IIV in Q, IIV in VC)[e]			0.059	60
cov(IIV in VP, IIV in CL)[e]			0.085	19
cov(IIV in VP, IIV in VC)[e]			0.072	27
cov(IIV in VP, IIV in Q)[e]			0.28	31
Proportional Residual Error			0.056	3.8
Additive Residual Error			0.15	71

[a] Eta shrinkage: ETA CL: 19.6%, ETA VC: 49.6%, ETA Q: 60.7%, ETA VP: 48.9%, ETA KA: 83.0%, ETA F1: 55.3%; Epsilon Shrinkage: Proportional: 14.3%, Additive: 13.8%

[b] $CL_{TV,ref}$, $VC_{TV,ref}$, $VP_{TV,ref}$, and $F1_{TV,ref}$ are typical values of CL, VC, VP, and F1at the reference covariate values. Covariate effects were estimated relative to a reference 50 year old RA patient who is male, weighing 70kg, with a calculated GFR of 90 mL/min/1.73m^2, baseline albumin level of 4.0 g/dL, swollen joint count of 16, not on NSAIDs and administered the Phase 3 SC formulation)

[c] $$CL_{TV} = CL_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{CL_{BWT}}\left(\frac{AGE_b}{AGE_{ref}}\right)^{CL_{AGE}}\left(\frac{ALB_b}{ALB_{ref}}\right)^{CL_{ALB}}\left(\frac{CGFR_b}{CGFR_{ref}}\right)^{CL_{cGFR}} \times \left(\frac{SWOL_b+1}{SWOL_{ref}+1}\right)^{CL_{SWOL}} \times exp(SEX \times CL_{SEX} + NSAID \times CL_{NSAID} + DISEASE \times CL_{DISEASE})$$

$$VC_{TV} = VC_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VC_{BWT}}$$

$$VP_{TV} = VP_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VP_{BWT}}$$

$F1_{TV} = F1_{TV,ref} + FORM \times F_{FORM}$ where F_{FORM} is the effect of SC formulation (Phase 2) on bioavilability

[d] Typical value for F1 is not the absolute bioavailability, $F_{absolute}=1/(1+\exp(-F1-F_{IIV}))$. At the reference value $F_{Absolute} = 78.6\%$.

[e] The calculated correlation coefficients (r^2) of the off-diagonal omegas were as follows: 0.32 for cov(IIV in VC, IIV in CL), 0.21 for cov(IIV in Q, IIV in CL), 0.12 for cov(IIV in Q, IIV in VC), 0.21 for cov(IIV in VP, IIV in CL), 0.22 for cov(IIV in VP, IIV in VC), 0.51 for cov(IIV in VP, IIV in Q)

The covariate-parameter relationship of disease (PsA vs. RA) on CL was assessed with the likelihood ratio test (LRT) for backward elimination. Since inclusion of this covariate-parameter relationship resulted in a decrease in the objective function value of -17.505 (P value $2.866 \cdot 10^{-5}$), it was retained in the full model and backward elimination was not performed. Therefore, the final model was equivalent to the full model.

Diagnostic plots of the final model are presented in Figure 5 and Figure 6, where the results for the pooled studies are stratified by administration route. The final model appropriately characterized the PK of abatacept, with slight overprediction of abatacept concentrations below 1 µg/mL (Figure 5) and slight overpredictions at high concentrations after SC administration (Figure 6).

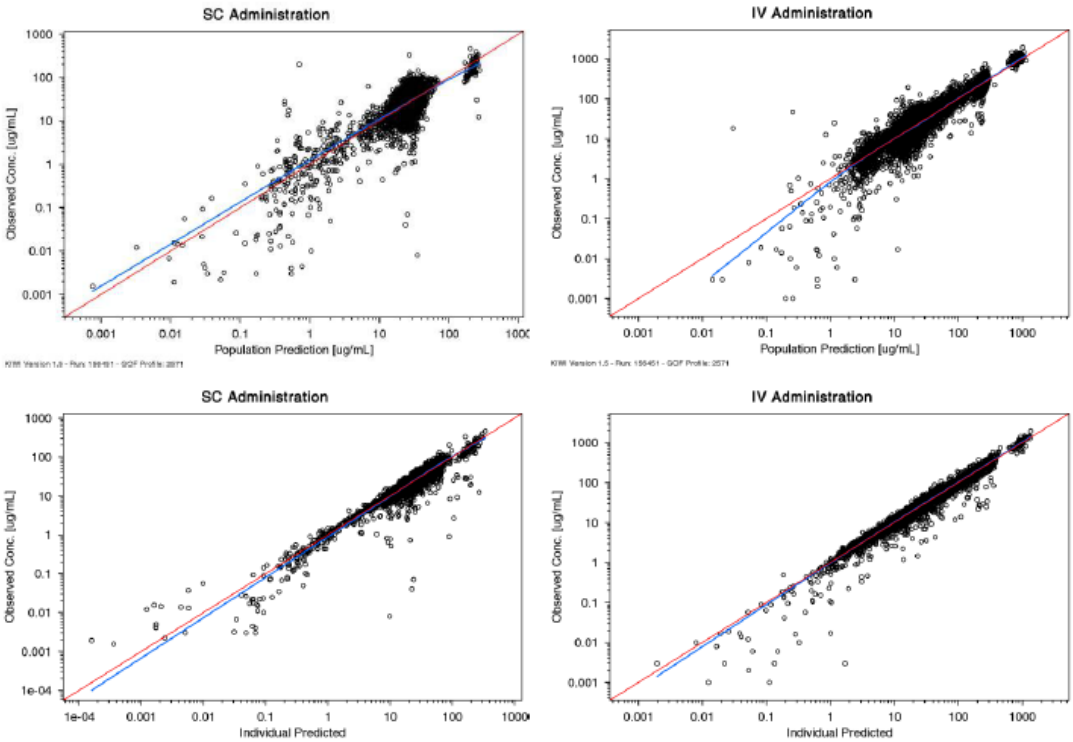


Figure 5 - Observed vs. Population Predicted and Individual Predicted Concentration by Administration Route (Final PPK Model, Log Scale)

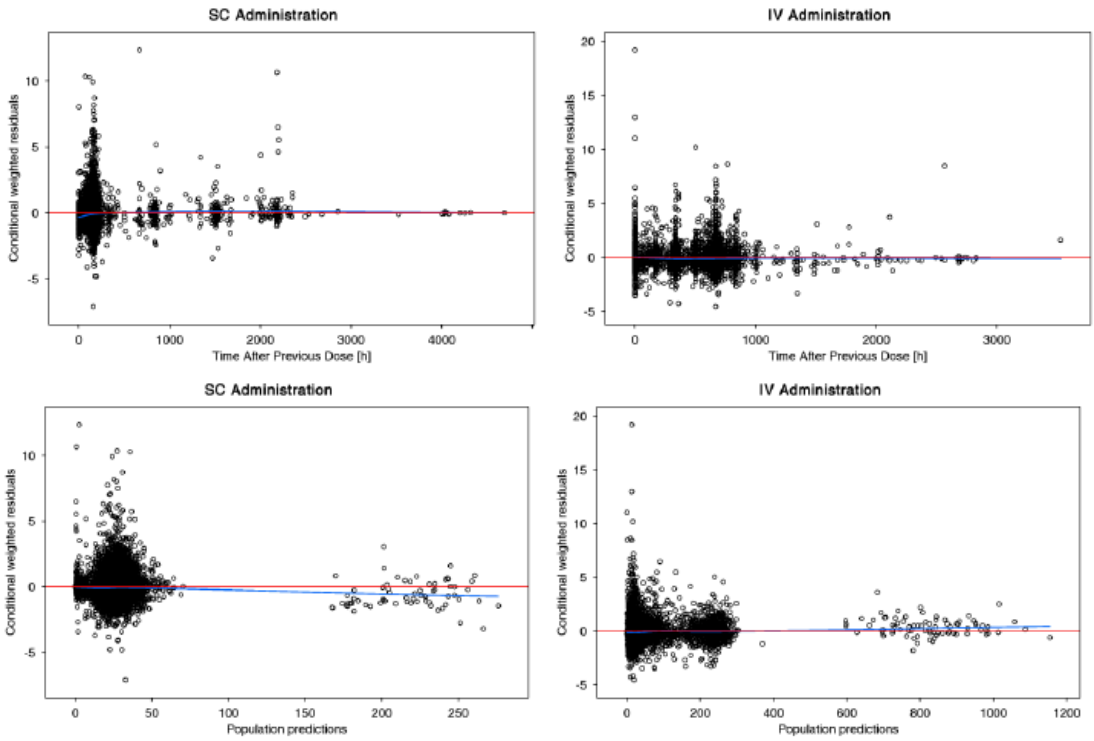


Figure 6 - CWRESI vs. time after previous dose (Top row) and CWRESI vs. predicted (Typical) serum concentrations (Bottom row) (Final PPK Model)

Evaluation of the final model using pcVPC showed that most of the observed abatacept serum concentrations fell within the 90% prediction interval, indicating that the final model adequately

described abatacept concentration-time profiles (Figure 7). pcVPC plots stratified by disease and administration route also indicated that the model was able to describe the observed data.

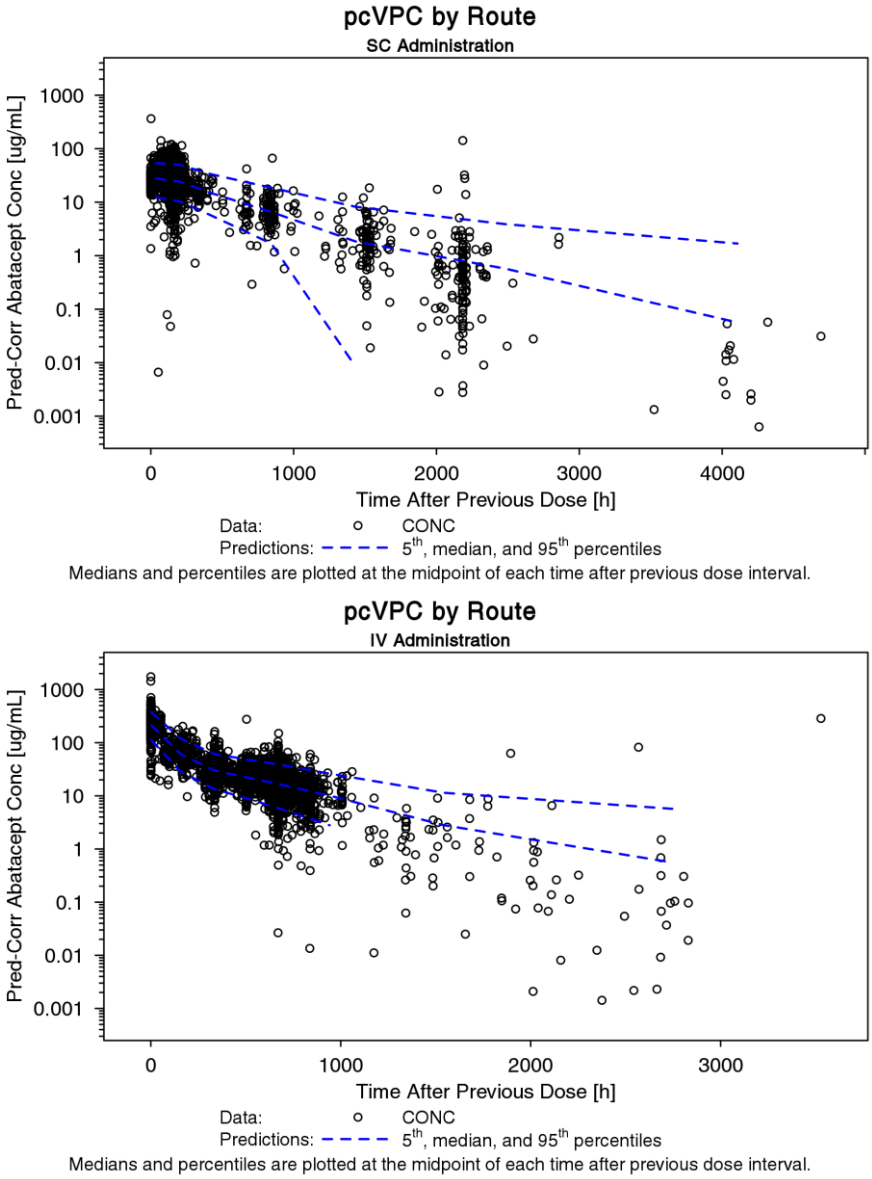


Figure 7 - Prediction corrected visual predictive check of concentration versus time after previous dose, stratified by route (final PPK model)

Graphical representations of the effect of covariates on the typical value of structural model parameters are presented in Figure 8. The estimated covariate effects (and 95% CI) are relative to CL, VC, or VP at the reference values of the covariates given in Table 9. The magnitude of all categorical covariate effects generally encompassed 80%-125% of reference values. The effect of baseline body weight was considered clinically relevant since its effect on the key parameters CL and VP exceeded the 80%-125% range. CL and VP increased with increasing baseline body weight. Although the effect of baseline body weight on VC was within the 80%-125% CI range, the 95% CI exceeded 125% suggesting that the relationship might be clinically relevant. All other covariate relationships were completely contained within the 80%-125% range and therefore not considered to be clinically relevant.

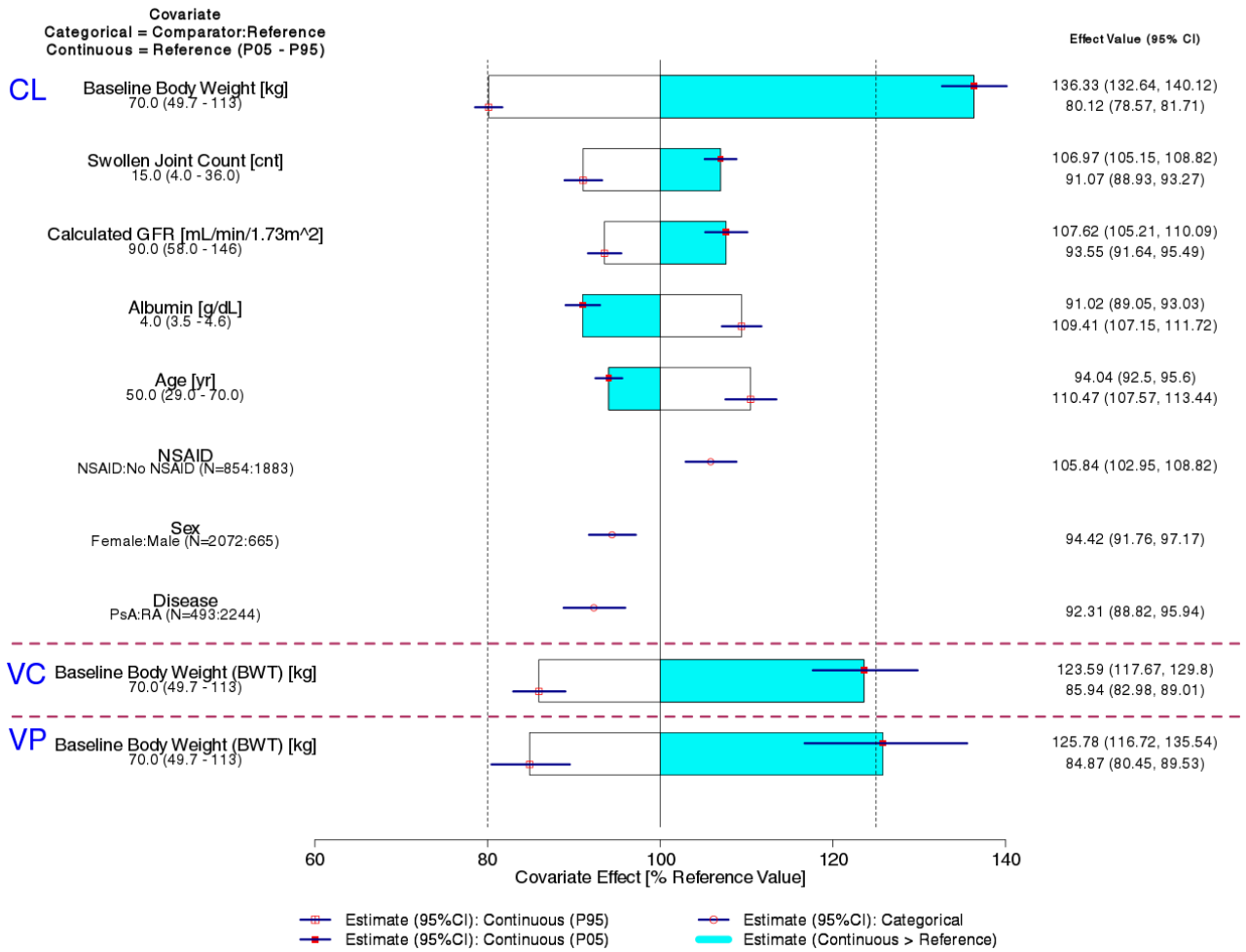


Figure 8 - Covariate effect forest plot based on the final PPK model

PK comparison by disease

The final PPK model was used to obtain maximum a posteriori (MAP) Bayesian estimates of the PK parameters and measures of exposure for each patient in the PPK analysis dataset. The estimated abatacept CL in PsA patients was about 8% lower relative to RA patients, which was within the pre-defined no-effect range of 80-125% (see Figure 9). Therefore, the effect of disease type was not considered to be clinically meaningful even though it was statistically significant. Overall, the estimated individual PK parameters of abatacept were comparable in RA and PsA patients (Table 10).

Table 10 - Summary statistics of predicted individual abatacept PK parameters for RA and PsA patients (PPK analysis set)

Parameter	RA Mean (Min, Max)	PsA Mean (Min, Max)
Clearance [mL/h/kg]	0.279 (0.0295, 0.69) (N = 2244)	0.235 (0.0831, 0.513) (N = 493)
Volume of Distribution of Central [L/kg]	0.0448 (0.0116, 0.0836) (N = 2244)	0.0397 (0.00942, 0.0579) (N = 493)
Intercompartmental CL [L/h]	0.0252 (0.00329, 0.137) (N = 2244)	0.0243 (0.00438, 0.084) (N = 493)
Volume of Dist. of Peripheral [L/kg]	0.059 (0.00333, 0.481) (N = 2244)	0.0526 (0.00781, 0.355) (N = 493)
Bioavailability	0.767 (0.0943, 1) (N = 1150)	0.77 (0.169, 0.885) (N = 365)
Absorption Rate Constant [1/h]	0.0118 (0.000988, 1.01) (N = 1150)	0.00855 (0.00386, 0.0257) (N = 365)
Alpha Half-life [day]	1.62 (0.566, 3.2) (N = 2244)	1.74 (1.11, 3.07) (N = 493)
Beta Half-life [day]	14.5 (4.53, 92.4) (N = 2244)	15.1 (7.08, 67.4) (N = 493)
Volume at Steady State [L/kg]	0.104 (0.015, 0.535) (N = 2244)	0.0923 (0.0233, 0.403) (N = 493)

Abbreviations: Max: maximum; Min: minimum; N: number of patients.

Boxplots of individual exposure estimates are displayed in Figure 9. Following s.c. administration the exposures were similar between PsA and RA patients. Following i.v. administration the exposures were generally slightly higher in patients with PsA compared to patients with RA.

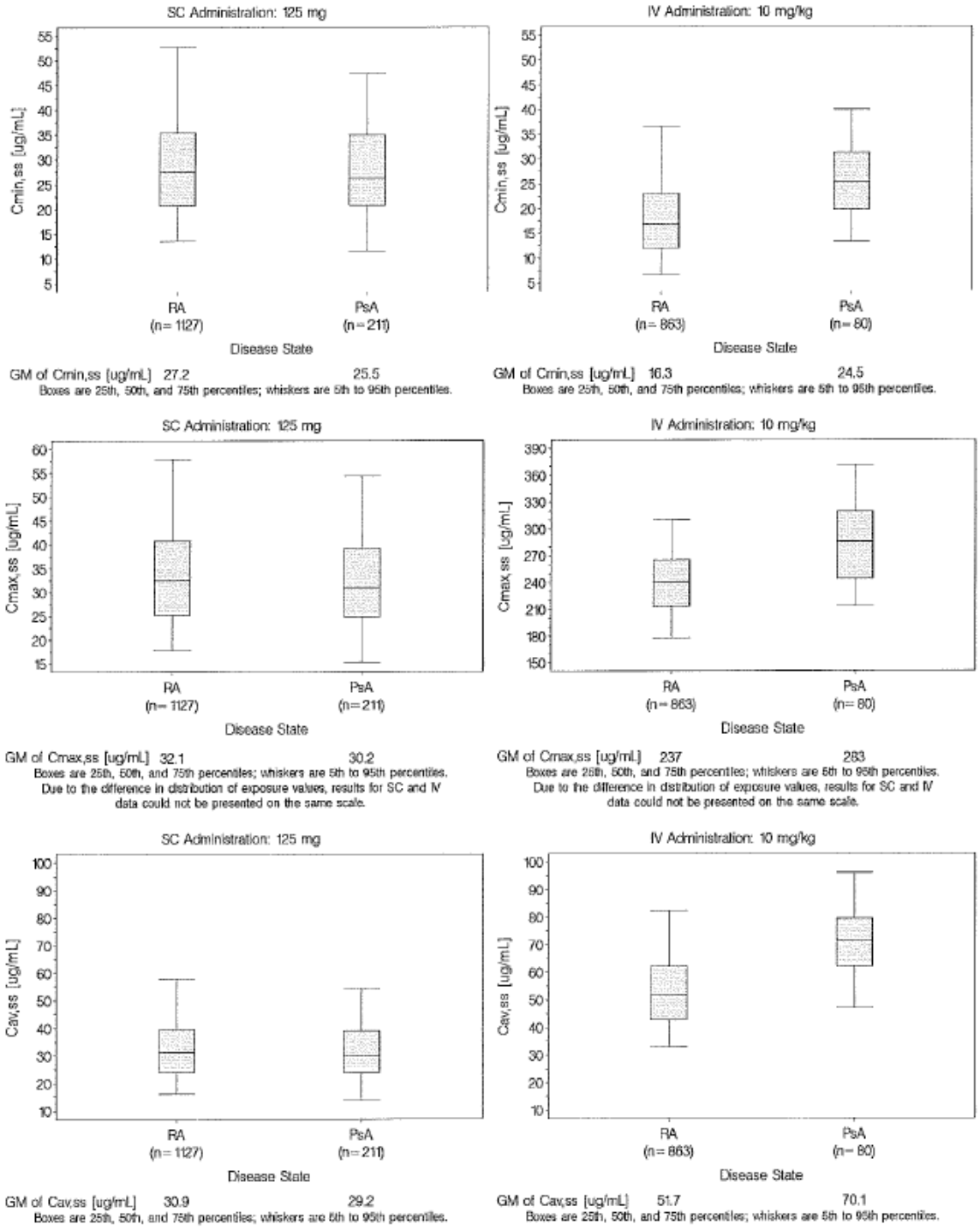


Figure 9 - Predicted abatacept C_{minss}, C_{maxss} and C_{avss} for RA and PsA patients by 125 mg s.c. weekly and 10 mg/kg i.v. monthly regimens

PK comparison in PsA patients by route of administration

The PK parameters for abatacept as estimated from the final PPK model are summarized in Table 11. No clinically meaningful differences were observed between i.v. and s.c. dosing in PsA patients.

Table 11 - Summary statistics of predicted individual abatacept PK parameters for PsA patients (PPK final model)

Parameter	IV[a] Mean (Min, Max)	SC (125 mg) Mean (Min, Max)
Clearance [mL/h/kg]	0.199 (0.0831, 0.398) (N = 128)	0.247 (0.103, 0.513) (N = 365)
Volume of Distribution of Central [L/kg]	0.0359 (0.00942, 0.0576) (N = 128)	0.041 (0.0247, 0.0579) (N = 365)
Intercompartmental CL [L/h]	0.0202 (0.00438, 0.0352) (N = 128)	0.0257 (0.0102, 0.084) (N = 365)
Volume of Dist. of Peripheral [L/kg]	0.0427 (0.00781, 0.0972) (N = 128)	0.0561 (0.0174, 0.355) (N = 365)
Bioavailability	NA	0.77 (0.169, 0.885) (N = 365)
Absorption Rate Constant [1/h]	NA	0.00855 (0.00386, 0.0257) (N = 365)
Alpha Half-life [day]	1.82 (1.22, 3.07) (N = 128)	1.71 (1.11, 2.43) (N = 365)
Beta Half-life [day]	15.1 (8.02, 25.3) (N = 128)	15.1 (7.08, 67.4) (N = 365)
Volume at Steady State [L/kg]	0.0787 (0.0233, 0.148) (N = 128)	0.0971 (0.0444, 0.403) (N = 365)

[a] Includes subjects on 3 mg/kg, 10 mg/kg, and 30/10 mg/kg.

Abbreviations: Max: maximum; Min: minimum; N: number of patients; NA: not applicable.

Stochastic Simulations in PsA population: Pharmacokinetic comparability

Simulations of abatacept steady-state concentration versus time profiles were performed for 2000 virtual PsA patients. Median steady-state abatacept serum concentrations vs. time profiles for 10 mg/kg i.v. and 125 mg s.c. are shown in Figure 10by weight tiers. While the 2 routes of administration provide different PK profiles, C_{minss} is approximately similar following administration of abatacept weight-tiered 10 mg/kg i.v. and 125 mg s.c. in patients with PsA.

Since body weight was identified as a significant covariate on the CL of abatacept, predicted exposures were stratified by body weight groups (Figure 11). For i.v. abatacept, the C_{minss} was similar in all 3 body weight groups, but C_{maxss} and C_{avss} increased as body weight increased. For s.c. abatacept, C_{min}, C_{max} and C_{avg} decreased as body weight increased. Model-based simulations predicted 125 mg s.c. weekly and 10 mg/kg i.v. elicited steady-state trough concentrations at or above 11.8 µg/mL and 8.5 µg/mL, respectively in 95% of PsA patients in the total population (Table 12).

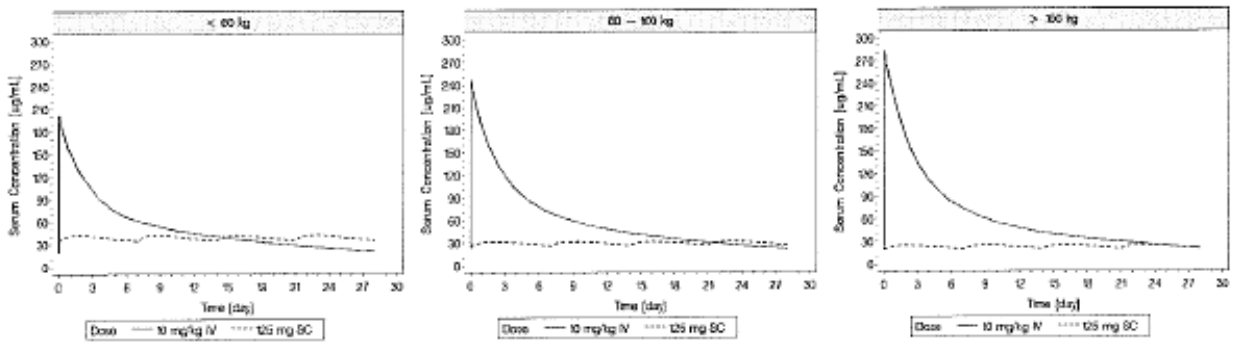


Figure 10 - Model-predicted median steady-state abatacept serum concentration (µg/ml) vs. time (days) profiles following monthly i.v. (10 mg/kg body-weight tiered doses) and weekly s.c. (125 mg dose) administered by body weight groups

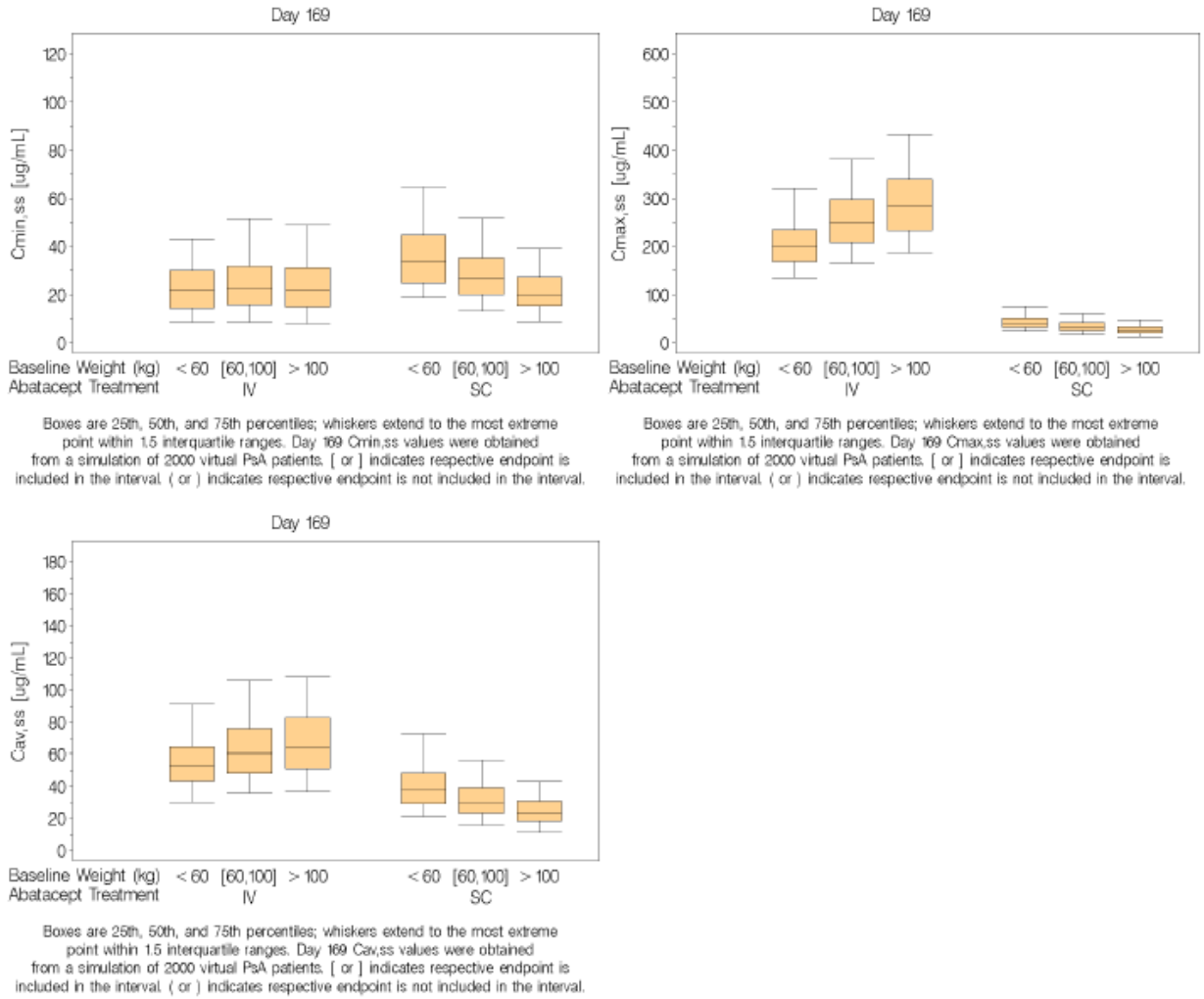


Figure 11 - Boxplots of Simulated Abatacept C_{minss} , C_{maxss} and C_{avss} on Day 169 by Baseline Body Weight for Virtual PsA Patients Administered 10 mg/kg i.v. and 125 mg s.c.

Table 12 - Summary statistics of abatacept C_{minss} by body weight groups for virtual PsA patients administered 10 mg/kg i.v. and 125 mg s.c.

Body Weight Groups	IV [µg/mL] Median (5th - 95th percentile)	SC [µg/mL] Median (5th - 95th percentile)
< 60 kg	21.8 (8.46 - 43.1)	33.6 (18.7 - 64.6)
60 - 100 kg	22.7 (8.61 - 51.5)	26.6 (13.1 - 51.6)
> 100 kg	21.5 (7.8 - 48.8)	20.1 (8.83 - 39)
Total	22.3 (8.46 - 50.5)	25.5 (11.8 - 51.3)

Abbreviations: IV: intravenous; kg: kilogram; mg: milligram; N: number of patients; SC: subcutaneous; µg/mL: micrograms per milliliter.

PPK analysis

- The PK of abatacept is time-invariant and can be described by a linear 2-compartment model with zero-order IV infusion, first-order absorption for SC administration, and first-order elimination.
- The PK of abatacept is similar in RA and PsA patients; abatacept CL in patients with PsA was approximately 8% lower relative to patients with RA. Overall, this resulted in slightly higher abatacept exposures in patients with PsA. This difference in exposures, however, was not considered to be clinically meaningful.
- Body weight was the only significant covariate identified to have a clinically meaningful impact on exposure.
- As expected, the s.c. 125 mg per week dosing regimen resulted in steady-state C_{min} concentrations similar to the i.v. 10 mg/kg monthly weight-tiered regimen in PsA patients.
- Model-based simulations predict that 125 mg s.c. weekly and 10 mg/kg i.v. elicited steady-state trough concentrations at or above 11.8 µg/ mL and 8.5 µg/mL, respectively, in 95% of patients across all body weights in PsA patients.

Stochastic Simulations

Abatacept 125 mg s.c. weekly and 10 mg/kg i.v. monthly delivered similar C_{minss} in PsA patients.

Exposure-Response (E-R) model

The selection of doses to test in the Phase 2 (IM101158) and Phase 3 (IM101332) PsA studies were based on the clinical experience in RA given the similarities between the 2 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 E-R relationship in RA suggested that C_{minss} 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. Furthermore, the s.c. formulation was shown to be therapeutically equivalent to the i.v. formulation based on an E-R rationale. While the 2 routes of administration provide different PK profiles, both i.v. (10 mg/kg weight-tiered dosing regimen administered monthly) and the s.c. (fixed dose of 125 mg administered weekly) delivered C_{minss} concentrations of 10 µg/mL and higher in patients across all body weights.

The dose-response relationship in PsA, following i.v. administration, showed that near maximal efficacy in terms of ACR20 was achieved with the 10 mg/kg weight-tiered monthly regimen. Furthermore, over 90% of patients with PsA achieved C_{minss} of 10 µg/mL with i.v. administration of 10 mg/kg monthly. Given the similarities in the disease states, it was reasonable to assume that the E-R relationships would be the same between RA and PsA, thereby rationalizing the selection of the 125 mg weekly s.c. dosing regimen for the Phase 3 PsA study.

Datasets

The E-R efficacy analyses included data from patients in the intent-to-treat (ITT) population with PsA from the double-blind portion of Studies IM101158 and IM101332. The E-R safety analyses included data from patients in the as-treated population with PsA from the double-blind portion of Studies IM101158 and IM101332. The analyses were performed with combined data from these 2 studies to enable assessment of abatacept exposure measures most relevant for clinical outcomes applicable to both routes of administration.

The PPK model-predicted exposure variables (C_{minss}, C_{maxss}, and C_{avss}) used for the E-R analysis of efficacy and safety were obtained by applying the individual parameter estimates from the final PPK model to the protocol-specified dose for that patient with the protocol-specified dosing interval were.

Separate NONMEM datasets were created and E-R models developed for each efficacy endpoint. The efficacy E-R analysis datasets included: Exposure variables; Response variables (ACR scores, PASI scores, DAS28-CRP scores, enthesitis scores, dactylitis scores, nail scores); Baseline demographic variables [age, gender, baseline body weight, race, and formulation (SC versus IV)]; Concomitant medication/treatment variables [MTX use (yes/no), corticosteroid (STER) use (yes/no), NSAIDs use (yes/no)]; Baseline tender joint count, baseline swollen joint count, baseline CRP, baseline physician global assessment, baseline psoriasis-affected BSA; Baseline disease characteristics for each endpoint (PASI, DAS28-CRP, enthesitis score, dactylitis score, nail score); Baseline duration of disease state (≤ 1 years, > 1 to 5 years, > 5 years to 10 years, > 10 years); Anti-TNF use (naive vs. prior users no longer on anti-TNF); Immunogenicity (ADA).

One record per patient was included in the E-R efficacy datasets for ACR scores, PASI scores, enthesitis scores, dactylitis scores, and nail scores at Day 169. However, the dataset for DAS28-CRP included all collected scores over time. Immunogenicity was treated as a stationary categorical covariate (positive/negative) in all the efficacy datasets.

Exploratory graphical E-R analyses of select safety endpoints (time to first autoimmune event, first infection, first serious infection, and first hypersensitivity reaction; binary AEs autoimmune event, infection, and local injection site reactions) were evaluated.

Two separate E-R datasets were built for time to event safety endpoints (first autoimmune event, first infection, first serious infection, and first hypersensitivity reaction) and binary adverse events (autoimmune event, infection, and local injection site reactions). The safety E-R analysis datasets included: Exposure variables; Response variables (i.e. the aforementioned safety endpoints); Baseline demographic variables (age, gender, baseline body weight, race); Immunogenicity (ADA).

One record per patient per adverse event was included in the E-R safety datasets.

Methods

Separate E-R models were developed for the following efficacy endpoints: ACR20, ACR50, and ACR70 at Day 169; PASI50 and PASI75 at Day 169; and DAS28-CRP scores (time-course and E-R) collected over 6 months following the initiation of treatment.

The E-R relationships between abatacept exposure and binary efficacy endpoints (ACR20, ACR50, ACR70, PASI50, and PASI75) were described by logistic regression models and included assessments of the effect of covariates on these E-R relationships.

The time-course and E-R relationship between abatacept exposure and DAS28-CRP scores were described by a mixed effects inhibitory maximum pharmacologic effect (E_{max}) model with respect to time and abatacept exposure and included assessment of the effect of covariates on the E-R relationship.

Given the large number of covariates evaluated as predictors of efficacy, graphical displays of the empirical logits versus continuous covariates were used to determine the functional form of each covariate to be tested. For categorical covariates tested in the analysis, the number of patients in each category was required to exceed 10% of the total number of patients. For race, all non-white patients were combined into a single category due to small sample size in nonwhite categories.

A single round of forward selection was then used to select covariates determined to be statistically significant when evaluated univariately using an alpha level of 0.01 for inclusion in the full model (decrease in the objective function of 6.64 with 1 df). The final model for each efficacy endpoint was developed from the full model by backward elimination of the covariate effects included in the full model. The backward elimination was used to determine a parsimonious model, based upon likelihood ratio test (LRT). A significance level of 0.001 was used for the backward elimination, corresponding to an increase in the objective function of 10.83 or 13.82, for 1 or 2 degrees of freedom, respectively.

Two methods of model evaluation were applied to ACR and PASI E-R models: the Hosmer-Lemeshow goodness-of-fit test and the area under the ROC curve. It was assumed that uncertainty in the final DAS28-CRP E-R model parameters was small relative to other sources of variability and the adequacy of the final model was evaluated using a simulation-based, VPC method. The final model was used to simulate 1000 replicates of the analysis dataset with NONMEM.

Stochastic simulations were performed to address the following issues: 1) predicting efficacy response following a lower SC dose (50 mg SC weekly) than previously tested; 2) bridging efficacy response comparing tiered weight-based i.v. administration of 10 mg/kg with 125 mg weekly s.c. dosing; and 3) therapeutic equivalence in efficacy response rate comparing IV and SC administration routes in the PsA population.

Results: E-R Efficacy analyses

E-R analysis: ACR20, ACR50 and ACR70

The E-R analyses of ACR20, ACR50, and ACR70 on Day 169 after abatacept or placebo dose were conducted with data from patients (N = 592) in PsA studies IM101158 and IM101332 for whom measures of abatacept exposure were available or who were randomized to receive placebo. The ACR20 score at 6 months was the primary endpoint in the Phase 3 clinical study, and therefore the E-R with respect to this endpoint was of particular interest.

ACR20

The drug effect E_{max} function was estimated with low precision (> 130% SEM) on the abatacept C_{minss} at which 50% of the maximal response (C50) parameter. There was a correlation between E_{max} and C50 (r^2 = 0.85). Given this, the drug effect model was re-evaluated. Logistic regression models for the probability of ACR20 response were used to evaluate abatacept exposure measures (C_{maxss}, C_{minss} and C_{avss}) as predictors of the E-R relationship using three functional forms: no effect, linear, or hyperbolic (E_{max}) effect.

The existence of a statistically significant E-R relationship for ACR20 was confirmed by comparing the results of the model with the logit as a function of exposure to a model in which the logit was not related to exposure (Table 13). Although C_{avss} as an E_{max} function showed slightly better decrease in the objective function than C_{minss} as an E_{max}, it did not provide a much better data fit. Therefore, and to be consistent with the exposure measure used in the previous RA analysis, the model with C_{minss} as an E_{max} function was selected for inclusion in the base model as it described the data in PsA patients well, especially at the highest exposure measures.

Table 13 - Summary of ACR20 Base Model Exposure Assessment

Exposure Measure	Functional Form	Ver	Change in VOF[a]	df	*P*-value[b]
Reference Model Filename: acr20-int-only.ctl (VOF=744.546)[c]					
Cavss	Emax	01	-25.284	2	3.234E-06
Cminss	Emax	01	-24.735	2	4.255E-06
Cmaxss	Emax	01	-24.034	2	6.041E-06
Cminss	Linear	01	-20.239	1	6.835E-06
Cavss	Linear	01	-13.104	1	2.947E-04
Cmaxss	Linear	01	-5.994	1	1.436E-02

[a] Change in the value of the objective function relative to the reference model

[b] Statistical significance ($\alpha = 0.05$)

[c] The reference model is an intercept only model in order to determine statistical significance of abatacept exposure.

Abbreviations: df: number of degrees of freedom associated with this addition to the model; Ver: version number of the control stream; VOF: value of the objective function.

MTX use as an exponential function and weight as a linear function were the only statistically significant covariates in the forward selection step and they were included in the full model. In the subsequent univariate backward elimination step each covariate was removed separately and evaluated for statistical significance. Only the effect of MTX use was statistically significant and was retained in the final model.

The final logit model for the probability of ACR20 response was an E_{max} function of C_{minss} and an additive effect of MTX use (Table 14). The Hosmer Lemeshow goodness of fit statistic was 4.38 with 8 degrees of freedom (P = 0.8211). The area under the ROC curve was 0.66, indicating a reasonable fitting and predictive model.

Table 14 - Final Model for the Probability of ACR20 Response

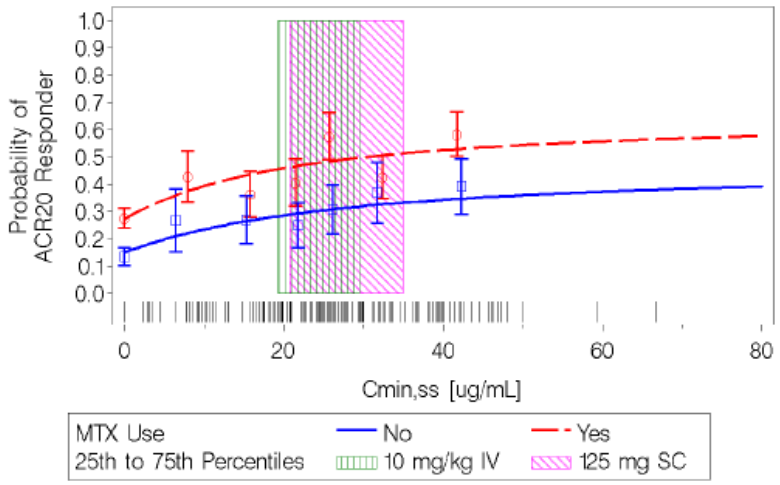
	Final Parameter Estimate	
Parameter	Typical Value	%SEM
INT: Intercept of Logit for All Patients	-0.987	16.5
EMAX: Maximum Response in Logit for Cminss[a]	1.60	52.9
C50: Aba Cminss Producing 50% of Emax in Logit (µg/mL)	19.0	133
COV1: Additive Shift for No MTX Use	-0.748	25.7
Minimum value of the objective function = 703.995		

[a] The following parameter estimates were found to be highly correlated (r^2 >= 0.810): (C50: Aba Cminss producing 50% of Emax in logit (µg/mL), EMAX: Maximum response in logit for Cminss)

Abbreviations: %SEM: standard error of the mean expressed as a percentage; Aba: abatacept.

The placebo effect, -0.987 on the logit scale, corresponds to a model-predicted probability of ACR20 response of 0.15 and 0.27 in the absence and presence of MTX use, respectively. For patients receiving

abatacept, at the median C_{minss} (26 µg/mL) the model-predicted probability of ACR20 is 0.48 and 0.31 with and without MTX use, respectively. There is a lack of effect of MTX use on placebo corrected ACR20 response since MTX use affects the model-predicted probability of ACR20 response in placebo patients and patients receiving abatacept similarly (ie, differences between placebo and 125 mg SC (median C_{minss}) of 0.21 with MTX use and 0.16 without MTX use). At the observed 25th to 75th percentile range of C_{minss} for 125 mg s.c. and 10 mg/kg i.v. abatacept, the probability of ACR20 response was approaching a plateau (Figure 12). The model-predicted probabilities of ACR20 response by MTX use for 10/10 mg/kg IV and 125 mg SC abatacept are provided in Table 15. The C_{minss} percentiles for 10/10 mg/kg IV and 125 mg SC were similar with a similar model-predicted probability of ACR20 response.



The lines represent the model−based predicted probability of ACR20 responder. The circles and squares represent the median Cmin,ss of the grouped data and associated observed probabilities. The bars around the circles and squares represent the standard errors of the observed proportions. The hash marks near the x−axis representthe individual Cmin,ss for ACR20 responder.

Figure 12 - Probability of ACR20 response at day 169 versus C_{minss}, by MTX use (Final model)

Table 15 - Predicted Probability of ACR20 Responses at day 169 (Final Model)

Dose (mg)	Cminss Percentile	Cminss [µg/mL]	With Concomitant Methotrexate ACR20	Without Concomitant Methotrexate ACR20
10/10 mg/kg IV	5%	13.77	0.42	0.26
	50%	25.21	0.48	0.30
	95%	39.73	0.52	0.34
125 mg SC	5%	11.54	0.41	0.25
	50%	26.31	0.48	0.31
	95%	47.30	0.54	0.36

ACR50 and ACR70

C_{minss} as a linear function was the most statistically significant predictor of both ACR50 and ACR70. None of the covariates evaluated met the criteria for statistical significance for ACR50 and ACR70 in the forward selection step. The Hosmer Lemeshow goodness of fit statistic was 5.20 (8 df, P = 0.7360) and 5.08 (8 df,

P = 0.7485) and the area under the ROC curve was 0.60 and 0.61 for the final ACR50 and ACR70 model, respectively.

The final model-predicted probability of ACR50 and ACR70 response versus C_{minss} is presented in Figure 13 along with the observed proportion of ACR50 responders for groups of C_{minss}.

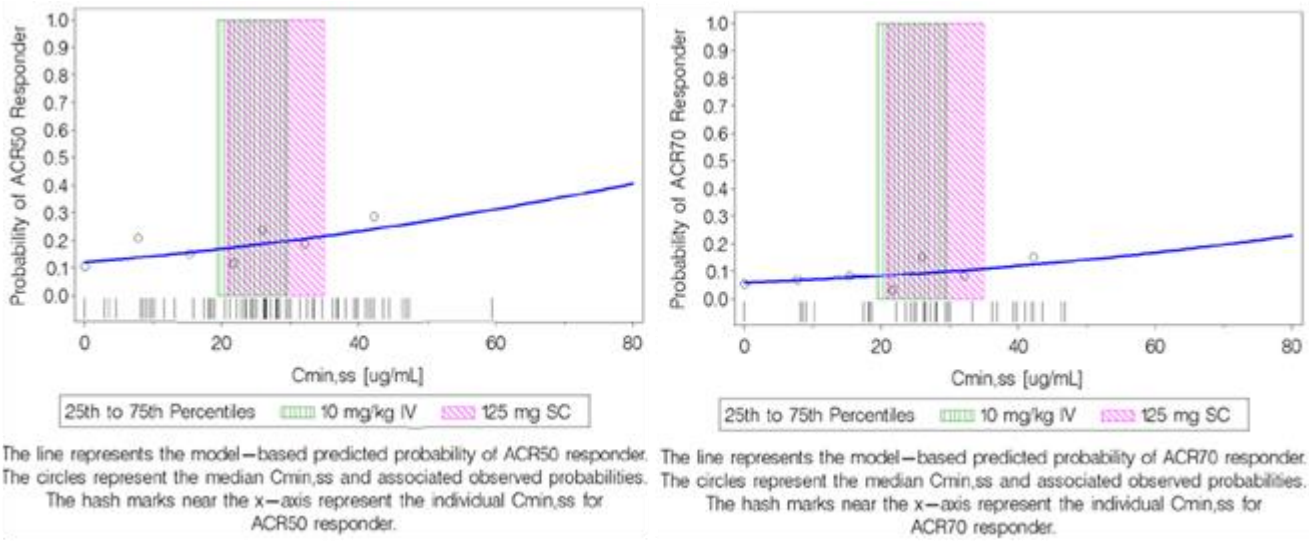
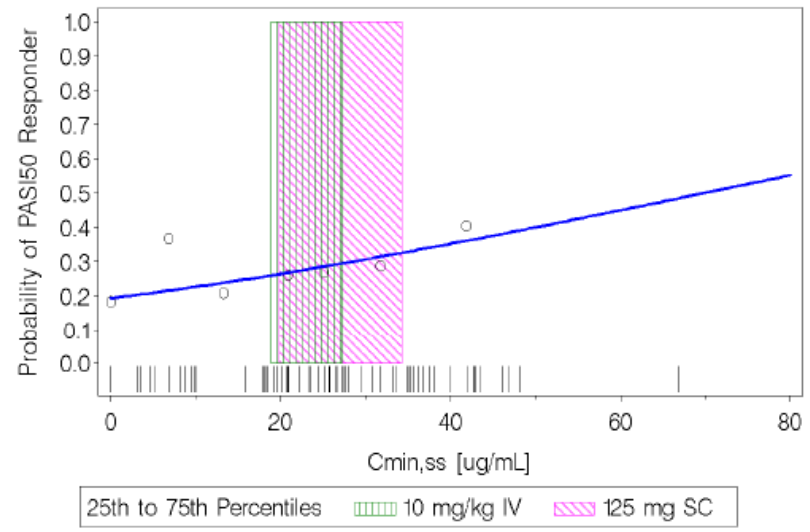


Figure 13 - Probability of ACR50 (left) and ACR70 (right) response at day 169 versus C_{minss} (Final models)

E-R analysis: PASI50 and PASI75

The E-R analyses of efficacy endpoints, PASI50 and PASI75, on Day 169 after abatacept or placebo dose was conducted with data from patients (N = 375) in PsA studies IM101158 and IM101332 for whom measures of abatacept exposure were available or who were randomized to receive placebo, and had a baseline psoriasis-affected body surface area (BSA) ≥ 3%.

C_{minss} as a linear function was used for PASI50 and PASI75. No covariates were identified to significantly influence the E-R for PASI responses. The probability of achieving PASI response at day 169 was found to increase with increasing C_{minss}. At the median C_{minss} (25 µg/mL and 24 µg/mL) from administration of 125 mg s.c. or 10 mg/kg i.v. abatacept, the model-predicted probability of PASI50 was 0.29 and 0.28, respectively. Similarly, assuming the median C_{minss} from administration of 125 mg s.c. or 10 mg/kg i.v. abatacept, the model-predicted probability of PASI75 was 0.17 and 0.16, respectively. The final model-predicted probability of PASI50 response versus C_{minss} is shown in Figure 14.



The line represents the model−based predicted probability of PASI50 responder. The circles represent the median Cmin,ss and associated observed probabilities. The hash marks near the x−axis represent the individual Cmin,ss for PASI50 responder.

Figure 14 - Probability of PASI50 response at day 169 versus C_{minss} (the final model)

E-R: DAS28-CRP

The E-R analyses of efficacy endpoint, DAS28-CRP (calculated using C-reactive protein, up to 6 months after first abatacept or placebo dose), was conducted with data from patients (N = 582) in PsA studies IM101158 and IM101332 for whom measures of abatacept exposure were available or who were randomized to receive placebo.

A non-linear mixed-effects inhibitory maximum pharmacological effect (E_{max}) model with respect to time was developed to characterize the E-R of abatacept exposure and DAS28. C_{minss} was the best measure of exposure for predicting the DAS28-CRP response with an E_{max} time-course model. The magnitude of the maximal decrease in DAS28-CRP increased with increasing C_{minss}. The prediction for the change from baseline in DAS28-CRP were -1.29 and -1.30, respectively, at doses 10 mg/kg i.v. and 125 mg s.c. weekly assuming median C_{minss}, greater than that from the placebo arm, -0.83. The scatterplot of the observed change in DAS28-CRP scores from baseline versus C_{minss} with the final model-predicted line overlaid is presented in Figure 15.

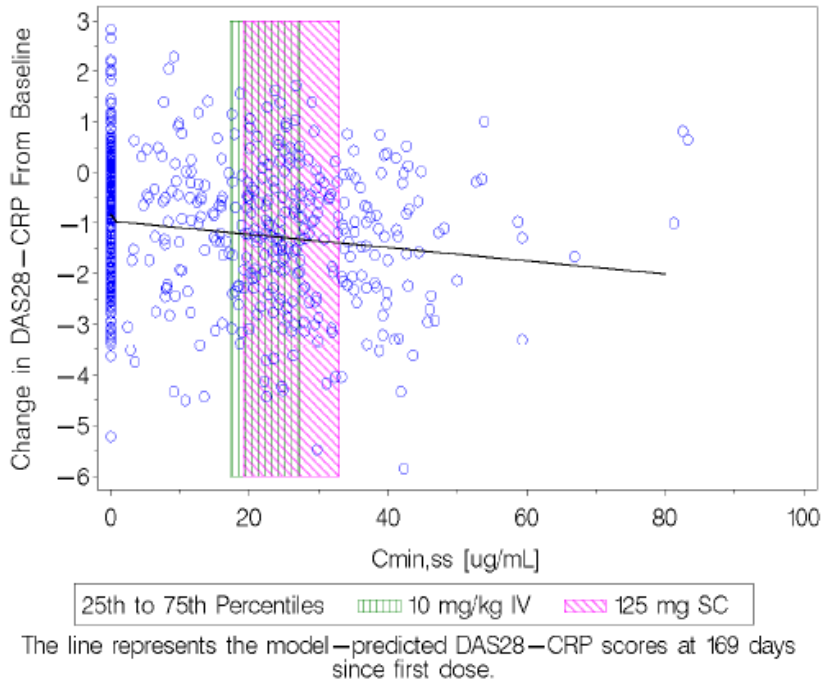


Figure 15 - Scatterplot of last observed change in DAS28-CRP from baseline at 6 months versus abatacept C_{minss} with model-predicted line overlaid

The model was parameterized in terms of baseline DAS28-CRP (BL), maximum reduction in DAS28-CRP score (EMX0), and T50. Additive IIV on BL and E_{max} were included. Exponential IIV was included on T50. An additive residual error model was used. The covariate analysis showed that the baseline DAS28-CRP (BL) increased with increasing baseline SWOL, baseline CRP, and baseline tender joint count. No statistically significant covariate effects were found on either the E_{max} or T50 parameters.

The scatterplot of observed DAS28-CRP scores versus days since first dose with the final model-predicted lines overlaid for each dose is shown in Figure 16.

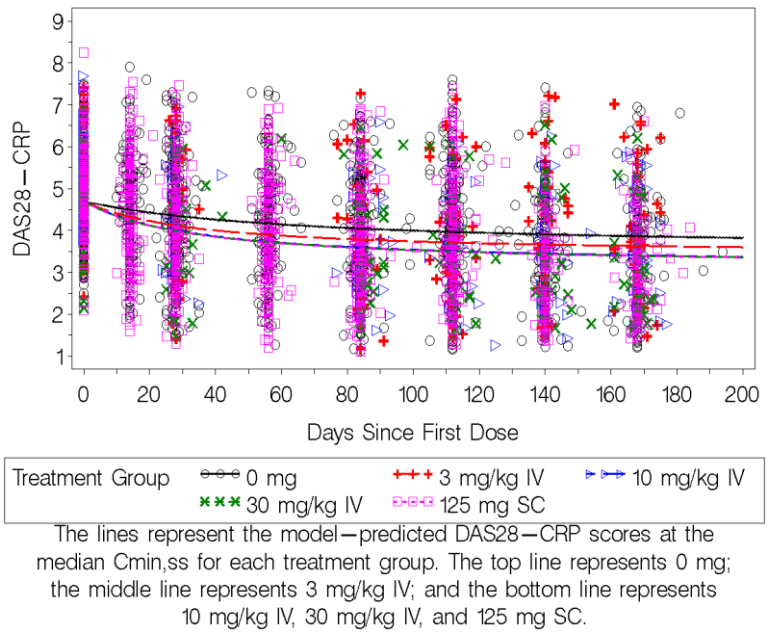


Figure 16 - Scatterplot of observed DAS28-CRP scores versus days since first dose with model-predicted line overlaid

Graphic analysis: Enthesitis, dactylitis and nail scores

Enthesitis scores were collected in studies IM101158 and IM101332 and were presented together. Dactylitis scores were collected differently in the studies and separate plots were created by study. Nail-visual analogue scale (VAS) scores were only available in study IM101332.

The exploratory graphical analyses showed that there appears to be a shallow decrease in enthesitis scores with increasing exposure to abatacept, with a slightly more evident trend in study IM101158 than in study IM101332.

For study IM101158, there also appeared to be a slight decrease in the change from baseline dactylitis scores with increasing exposure to abatacept. However, there appeared to be no relationship between dactylitis and abatacept exposure in study IM101332.

In Study IM101332, as abatacept exposure increased, nail-VAS scores decreased on day 169.

When comparing C_{min} steady-state (median ~26 µg/mL) following administration of the 10 mg/kg i.v. and 125 mg s.c. dosing to placebo, there were numerical improvements in enthesitis, dactylitis and nail-VAS scores (study IM101332) and enthesitis and dactylitis (study IM101158).

Graphic analysis: Time to event Safety results

The E-R analyses of time to event safety endpoints (first autoimmune event, first infection, first serious infection, and first hypersensitivity reaction) and binary adverse events (autoimmune event, infection, and local injection site reactions) were conducted with data from patients (N = 592) in PsA studies IM101158 and IM101332 (double blinded period) for whom measures of abatacept exposure were available or who were randomized to receive placebo.

The number of patients who had at least one occurrence of an autoimmune event, infection, serious infection, or hypersensitivity reactions was low (see Table 16).

Table 16 - Summary of first occurrence of adverse events in the E-R safety analysis

PD Endpoint		Placebo (N = 253)	3/3 mg/kg IV (N = 45)	10/10 mg/kg IV (N = 40)	30/10 mg/kg IV (N = 43)	125 mg SC (N = 211)	Overall (N = 592)
Autoimmune Adverse Event Occurrence, N (%)	No	251 (99.2)	45 (100.0)	37 (92.5)	43 (100.0)	211 (100.0)	587 (99.2)
	Yes	2 (0.8)	0 (0.0)	3 (7.5)	0 (0.0)	0 (0.0)	5 (0.8)
Infection Adverse Event Occurrence, N (%)	No	183 (72.3)	30 (66.7)	29 (72.5)	30 (69.8)	155 (73.5)	427 (72.1)
	Yes	70 (27.7)	15 (33.3)	11 (27.5)	13 (30.2)	56 (26.5)	165 (27.9)
Serious Infection Adverse Event Occurrence, N (%)	No	252 (99.6)	45 (100.0)	39 (97.5)	43 (100.0)	210 (99.5)	589 (99.5)
	Yes	1 (0.4)	0 (0.0)	1 (2.5)	0 (0.0)	1 (0.5)	3 (0.5)
Hypersensitivity Reaction Adverse Event Occurrence, N (%)	No	253 (100.0)	45 (100.0)	39 (97.5)	43 (100.0)	211 (100.0)	591 (99.8)
	Yes	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.2)

The model predicted distributions of C_{minss}, C_{maxss} and C_{avgss} of patients with at least one observed infection were comparable to the model predicted exposures of patients with no observed event.

Within the range of C_{minss}, C_{maxss}, C_{avgss} associated with the abatacept doses studied there was no apparent relationship between exposure and the probability of experience an infection.

Stochastic simulations

The probability of ACR20 response and PASI50 response on Day 169 was simulated using the virtual PsA patients' exposure measures and the final E-R models. Summary statistics of the simulated probability of ACR20 and PASI50 are shown in Table 17 by treatment regimen. The results for ACR20 are illustrated in Figure 17 stratified by MTX use and dosage. The model-predicted ACR20 response was similar between 10 mg/kg i.v. once monthly and 125 mg s.c. weekly; lower doses were predicted to provide inferior clinical response. Figure 18 provides the simulated probability of ACR20 versus C_{minss} with shaded regions representing the 90% prediction interval for the absence and presence of MTX use.

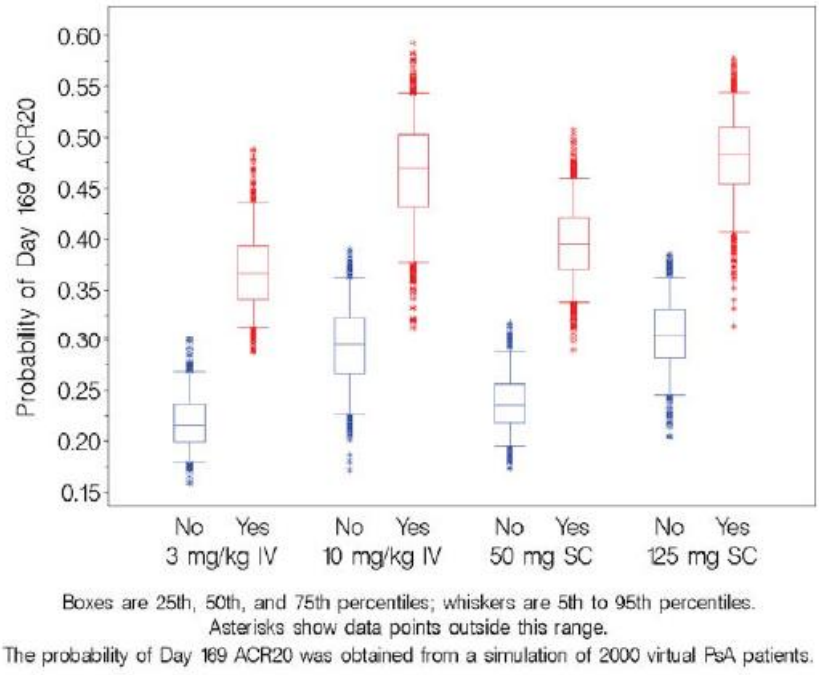
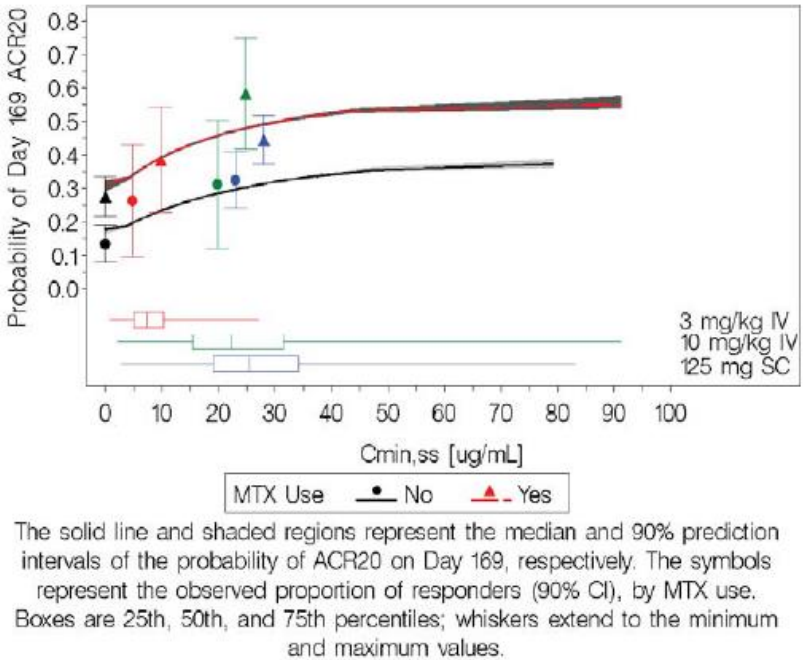


Figure 17 - Boxplots of Simulated Day 169 Probability of ACR20 Response



The solid line and shaded regions represent the median and 90% prediction intervals of the probability of ACR20 on Day 169, respectively. The symbols represent the observed proportion of responders (90% CI), by MTX use. Boxes are 25th, 50th, and 75th percentiles; whiskers extend to the minimum and maximum values.

Figure 18 - Observed and Simulated Probability of ACR20 vs. C_{minss} by Methotrexate Use and Boxplots of Simulated C_{minss}

Table 17 - Summary Statistics of Simulated Probability of Day 169 ACR20 and PASI50 Response by Treatment

Efficacy Endpoint		3 mg/kg IV (N = 2000)	10 mg/kg IV (N = 2000)	125 mg SC (N = 2000)
Probability of Day 169 ACR20	Mean (SD)	0.3135 (0.0801)	0.4024 (0.0952)	0.4152 (0.0933)
	Median	0.3353	0.4236	0.4478
	Min, Max	0.158, 0.488	0.172, 0.593	0.204, 0.578
Probability of Day 169 PASI50	Mean (SD)	0.2206 (0.0148)	0.2881 (0.0583)	0.2993 (0.0542)
	Median	0.2177	0.2746	0.2878
	Min, Max	0.196, 0.295	0.200, 0.691	0.203, 0.567

Abbreviations: IV: intravenous; kg: kilogram; Max: maximum; mg: milligram; Min: minimum; N: number of patients; SC: subcutaneous; µg/mL: micrograms per milliliter; SD: standard deviation.

E-R analyses of efficacy

- As seen in RA patients, an Emax model adequately described the E-R relationship for ACR20 in PsA patients.
- The C_{minss} was a statistically significant predictor of ACR20, ACR50, and ACR70 on day 169, as seen earlier with RA. The probability of ACR response at day 169 increased with increasing values of C_{minss}. Maximal ACR20 response was achieved within the observed C_{minss} range for the 10 mg/kg i.v. and 125 mg s.c. dosing regimens.
- MTX use was a statistically significant predictor of ACR20 on day 169 whereby the probability of ACR20 response increased with use of MTX by approximately 55% at the median C_{minss} associated with the 10 mg/kg i.v. monthly regimen (26 µg/mL) and 125 mg s.c. weekly regimen (26 µg/mL).

However, when the ACR20 responses relative to placebo were compared, MTX did not affect the ACR20 E-R relationship.

- E-R relationships for PASI50 and PASI75 were described by a linear function of C_{minss}; PASI response was achieved within the observed C_{minss} range for the 10 mg/kg i.v. and 125 mg s.c. dosing regimens.
- The C_{minss} was a statistically significant predictor of PASI50 and PASI75 on day 169. The probability of PASI response at Day 169 increased with increasing values of C_{minss}. Although not obtaining the maximal possible response, PASI50 response achieved noticeable numerical effect within the observed C_{minss} exposure.
- Baseline weight, age, baseline tender joint count, baseline SWOL, baseline CRP, baseline physician global assessment, baseline psoriasis-affected BSA, baseline DAS28-CRP, baseline PASI, baseline duration of disease, sex, race, formulation type, STER use, NSAID use, anti-TNF use, and ADA were not identified as statistically significant predictors of the probability of ACR20, ACR50, ACR70, PASI50, or PASI75 on Day 169 in patients with PsA. In addition, MTX use was not a significant predictor of the probability of ACR50, ACR70, PASI50, or PASI75 on day 169.
- The C_{minss} was a statistically significant predictor of DAS28-CRP scores over time. The magnitude of the maximal decrease in DAS28-CRP increased with increasing C_{minss}. The prediction for the change from baseline in DAS28-CRP were -1.29 and -1.30, respectively, at doses 10 mg/kg i.v. and 125 mg s.c. weekly assuming median C_{minss}, greater than that from the placebo arm, -0.83.
- No statistically significant influence of age, baseline weight, baseline physician global assessment, baseline psoriasis-affected BSA, baseline DAS28-CRP, baseline duration of disease, sex, race, formulation type, STER use, NSAID use, anti-TNF use, or ADA was found for DAS28-CRP scores.
- Across endpoints, including ACR20, ACR50, ACR70, PASI50, PASI75, and DAS28-CRP, the C_{minss} was identified as the best exposure predictor for efficacy.
- When comparing C_{minss} (median ~26 µg/mL) following administration of the 10 mg/kg i.v. and 125 mg s.c. dosing to placebo, there were numerical improvements in enthesitis, dactylitis and nail-VAS scores (Study IM101332) and in enthesitis and dactylitis (study IM101158).

Stochastic Simulations

- Abatacept 125 mg s.c. weekly provided similar response to 10 mg/kg i.v. once monthly in both ACR20 and PASI50 at 6 months.

2.3.5. Discussion on clinical pharmacology

The PK data of abatacept in PsA patients were obtained from 2 clinical studies. In addition simulated PK data from the PPK model and exposure-response (E-R) analysis data of efficacy and safety were presented.

Three analytical methods in IM101158 and IM101332 clinical studies have been used to assess the concentration of abatacept and anti-abatacept antibodies in human serum. The assays include an ELISA assay for quantification of abatacept, ECL assay for the detection of anti-drug antibodies (ADA), and an in-vitro assay for analysis of anti-drug neutralizing antibodies (NAb). In general, the bioanalytical assays used to quantitate abatacept and anti-abatacept antibodies as well as neutralizing antibodies in human serum samples were adequately described and appropriately validated.

However, some concerns were raised regarding the NAb assay. The in-vitro cell assay for neutralizing abatacept antibodies was validated using normal human serum matrix, having a final serum concentration of 4%. The assay was found tolerant for drug levels below 1 µg/mL. Therefore the clinical samples analysed in the Nab assay must have abatacept concentration ≤ 1 µg/mL. Drug interference

occurs at levels relevant in patient sera which clearly compromises the value of the assay. It is however concluded that the uncertainties related to the suitability of the Nab assay are not affecting the benefit/ risk profile of abatacept in the treatment of PsA. A post-approval recommendation was requested. For any future application for Orencia containing immunogenicity assessment, the MAH will improve the Nab assay, particularly the drug tolerance for abatacept levels more relevant in patients' sera.

In the clinical study IM101158, the studied abatacept doses were "30/10" mg/kg (by weight) "10/10" mg/kg (fixed dose), "3/3 mg/kg (by weight) and placebo as an i.v. infusion administered on days 1, 15, 29, 57, 85, 113 and 141 (= 20 weeks after infusion). The selected doses and time points for administration i.v. abatacept in this first clinical study in PsA patients were adequate on the basis of the earlier performed clinical studies with abatacept (e.g. in RA patients). The study included initially a double-blind short-term (ST) period of 6 month and thereafter an open-label (OL) long-term extension (LTE) period; however; the LTE period was prematurely terminated due to the modest efficacy on skin-related parameters. The planned population PK analysis was not performed because no additional information related to the PK would have been received. The mean C_{min} values with the dosing regimens "10/10" mg/kg and "30/10" mg/kg were greater (mean C_{minss} concentrations were 24-33 µg/ml) than the target abatacept steady-state concentration of ≥ 10 µg/ml. Whereas, the mean C_{minss} concentrations with "3/3" mg/kg regimen were ≤ 10 µg/ml. The C_{min} concentrations were similar level with "10/10" mg/kg and "30/10" mg/kg doses as earlier seen in the clinical studies with similar dosing regimen and route in RA patients. The variations in C_{min} values were moderate or great (CV%s of 29-57%). The C_{minss} concentrations were reached between day 57 and day 85 depending on the dose and this is consistent with the $t_{1/2}$ of abatacept of about 13 days (ranging from 8 to 25 days), as reported in RA patients. The PK of abatacept in PsA patients shows dose-proportional increases of C_{min} over the dose range of 3 mg/kg to 10 mg/kg.

In the clinical study IM101332, the first 24 weeks (169 days) were as double-blind and thereafter open-label (OL) up to 28 weeks. At the end of the OL period, patients had the option of entering a 1-year LTE period. In the double-blind period, patients received weekly s.c. abatacept 125 mg or placebo. During the OL and LTE period, all patients received weekly s.c. abatacept 125 mg. The C_{minss} concentrations were reached at day 57. The mean C_{minss} concentrations after abatacept 125 mg s.c. weekly remain between 28 µg/ml and 30 µg/ml in both ST period and OL/LTE periods. The variations in the C_{minss} concentrations were great (CV%s of 37-54%).

Conclusions related to the PK of abatacept from these 2 clinical studies (on the basis of the C_{min} concentrations) are that the exposure with 125 mg s.c. weekly is similar in PsA patients as in RA patients and with 10 mg/kg i.v. (administered on day 1, 2, 4 and every 4 weeks thereafter) and 125 mg s.c. weekly the similar exposure to abatacept are achieved.

On the basis of the PPK model, the PK of abatacept can be described by a linear 2-compartmental model with zero-order absorption for i.v. infusion and first-order absorption for s.c. administration, and first-order elimination. Abatacept CL was ~ 8% lower in PsA patients compared with RA patients. The effect of disease type on CL was statistically significant but not clinically meaningful. Body weight was the only covariate retained in the final PPK model: Abatacept CL and VP slightly increased with increasing weight, and a similar trend was observed for VC. Predicted systemic exposure (C_{minss}) of abatacept was overall comparable following s.c. (125 mg weekly) and i.v. administration (weight-based doses ~ 10 mg/kg monthly). As expected, patients with lower body weight had higher C_{minss} after fixed-dose s.c. administration than patients with higher body weight. Presence of anti-drug antibodies had no detectable impact on the CL of abatacept following i.v. or s.c. administration.

Conclusions from the E-R analyses were that C_{minss} was the best exposure predictor for efficacy responses (i.e. ACR, PASI, DAS28-CRP). The relationship between abatacept C_{minss} and ACR20 in PsA patients was

described with an E_{max} function, MTX use was included as an additive effect in the model. MTX use increased the probability of ACR20 response, however; the difference in ACR20 response of the abatacept group compared with the placebo group was similar (~ 20%) with and without MTX. No associations between estimated exposure to abatacept and selected safety parameters (e.g. any infection; serious infection; hypersensitivity reaction; autoimmune disorder) were observed. However, this should be interpreted with caution because serious adverse reactions were observed in only few patients.

The mechanism of action of abatacept in PsA is not completely clarified. Abatacept has greater efficacy in the joints vs. skin in PsA and the reason for this is thought to be the distinct pathologies with divergent roles of immune cells in skin versus synovial inflammation in PsA. T cells are thought to have a less important role in skin inflammation than in joint inflammation.

Relevant PK data for the adult PsA population obtained from both clinical studies and in agreement with the results of the PPK analysis has been included in section 5.2 of the SmPC.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of abatacept in PsA patients was comparable to PK in RA patients.

Regarding the NAb assay it was observed that drug interference occurs at levels relevant in patient sera which might compromise the value of the assay. It was although concluded that the uncertainties related to the suitability of the Nab assay do not put into question the benefit/ risk profile of abatacept in the treatment of PsA. However, CHMP recommended that for any future application for Orencia containing immunogenicity assessment the MAH should improve the Nab assay, particularly the drug tolerance for abatacept levels more relevant in patients' sera.

2.4. Clinical efficacy

2.4.1. Dose response study

A Phase IIB, Multi-Dose, Multi-Centre, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Abatacept Versus Placebo in the Treatment of Psoriatic Arthritis (Study IM101158)

Methods

Study IM101158 consisted of 2 study periods: a 6-month double-blind, placebo-controlled ST period and an open-label LT extension period for subjects who completed the ST period. Although the pre-specified primary objective was achieved for this study, namely, abatacept at doses of 30/10 mg/kg and 10/10 mg/kg demonstrated statistically superior ACR 20 response rates at Day 169 compared to placebo, the LT period of the study was prematurely terminated due to the modest efficacy on skin-related parameters. Notification of the intent to terminate this study was sent to all sites participating in the LT period in a letter dated 31-Aug-2010, and sites were instructed to discontinue treatment in all active subjects as of Jan-2011.

Subjects with PsA were evaluated during the screening period, and those who met all study eligibility criteria were stratified by percentage of psoriasis-affected BSA (≥ 3% vs < 3 %) and randomized on Day 1 in a 1:1:1:1 ratio to treatment with 1 of 3 regimens of abatacept (30/10 mg/kg, 10/10 mg/kg, 3/3 mg/kg) or placebo. During the ST period, study medication (abatacept or placebo) was infused IV in a double-blind manner on Days 1, 15, 29 and every 28 days thereafter. Subjects who completed the ST

period and entered the LT period received open-label treatment with abatacept at 10 mg/kg beginning at Day 169 for the remainder of the study.

Study participants

Key inclusion criteria:

- Men and women (not nursing or pregnant) at least 18 years of age at time of informed consent
- Met Classification Criteria for Psoriatic Arthritis (CASPAR) for a duration of disease of at least 3 months
- Had disease activity defined as a tender joint count of ≥ 3, swollen joint count of ≥ 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 prior failure on MTX must have been on a dose of at least 15 mg/week for a minimum of 2 months. Subjects with a recent failure of TNFα therapy must have undergone a minimum washout period (56 days for infliximab; 28 days for etanercept or adalimumab)
- Been able to have a MRI performed

Key exclusion criteria (summary):

- Scheduled for or anticipating joint replacement surgery
- Currently receiving treatment with molecular biologic therapies (including, but not limited to, TNFα blockers), leflunomide, mycophenolate mofetil, cyclosporine, and tacrolimus, D-penicillamine, cyclophosphamide, or immunoadsorption columns (such as Prosorba columns). A washout period was required for all medicinal agents listed above.
- Presence of concomitant illness likely to require systemic glucocorticosteroid therapy during the study, in the opinion of the investigator
- History or current evidence of malignancy
- At risk for tuberculosis
- Any serious bacterial infection within the last 3 months not treated or resolved with antibiotics, or any chronic bacterial infection
- Evidence of active or latent bacterial or viral infection(s) at the time of potential enrollment, including human immunodeficiency virus or herpes zoster or cytomegalovirus that resolved less than 2 months prior to enrolment.

A total of 48 sites participated; 46 sites enrolled and treated subjects in this study, including 19 sites in the US, 4 sites in Canada, 16 sites in Europe (4 sites in Germany, 4 sites in France, 3 sites in Italy, 2 sites in Belgium, 1 site in Spain, 1 site in The Netherlands, 1 site in Norway, 3 sites in Australia, 3 sites in Argentina, and 1 site in South Africa.

Treatments

Subjects received 1 of the following 4 treatments during the ST period:

- Abatacept 30/10 mg/kg regimen by IV infusion: abatacept 30 mg/kg (by weight) on Days 1 and 15 followed by abatacept (fixed dose) approximating 10 mg/kg on Days 29, 57,85, 113, and 141
- Abatacept 10/10 mg/kg regimen by IV infusion: abatacept (fixed dose) approximating 10 mg/kg on Days 1, 15, 29, 57, 85, 113, and 141
- Abatacept 3/3 mg/kg regimen by IV infusion: abatacept 3 mg/kg (by weight) on Days 1, 15, 29, 57, Days 85, 113, and 141
- Placebo (dextrose 5% in water [D5W]) or normal saline (NS) by IV infusion on Days 1, 15, 29, 57, 85, 113, and 141

During LT period, all participating subjects received a fixed dose of open-label abatacept approximating 10 mg/kg by IV infusion beginning on Day 169 and every 28 days thereafter.

The first 2 doses of study drug in the ST period were administered utilizing a "double-dummy" design, necessitated by the absence of stability data for concentrations of abatacept with the 3 mg/kg dosage and 30 mg/kg dosage. Specifically, all subjects received simultaneous 250 cc and 100 cc infusions. Beginning with the infusion on Day 29, all infusions were given in 100 cc of NS or D5W over 30 minutes.

Objectives

Objectives for the Short-term Period: Primary Objective

The primary objective of this study was to compare the efficacy of 3 regimens of abatacept versus placebo in a 6-month double-blind study of PsA, as measured by the proportion of subjects achieving an ACR 20 response at Day 169.

Objectives for the Short-term Period: Secondary objectives

- To estimate the difference in proportion of subjects achieving an Investigator Global Assessment (IGA) score of clear or almost clear in each of the 3 abatacept arms compared to placebo at Day 169
- To estimate the difference in mean percentage change from baseline in each of the 3 abatacept arms compared to placebo in target lesion scores at Day 169
- To estimate the difference in mean changes from baseline in physical and mental functions as measured by Short-Form 36 (SF-36) in each of the 3 abatacept arms compared to placebo at Day 169
- To estimate the difference in proportion of subjects with a diminution in disabilities as measured by Health Activities Questionnaire (HAQ) scores between the 3 abatacept arms placebo at Day 169
- To describe the safety, tolerability, immunogenicity, and to predict the pharmacokinetics (PK) of each of the 3 abatacept arms using population PK methodology

Objectives for the Long-term Period: Primary Objective

The primary objective of the LT period was to assess the safety and tolerability of abatacept treatment during the open-label extension phase (18 months after the initial 6-month, double-blind period).

Objectives for the Long-term Period: Secondary objectives

- To assess the proportion of subjects achieving an ACR 20, ACR 50, ACR 70, and ACR 90 responses at Days 365 and 729
- To assess the proportion of subjects achieving an IGA score of clear or almost clear at Days 365 and 729
- To assess the mean percentage change from baseline in target lesion scores at Days 365 and 729
- To assess the mean changes from baseline in the physical and mental functions as measured by SF-36 at Days 365 and 729
- To assess the proportion of subjects with a diminution in disabilities as measured by HAQ scores at Days 365 and 729

Exploratory objectives of the Phase 2 study IM101158 are not listed here.

Outcomes/endpoints

The primary efficacy outcome measure for the ST period was an ACR 20 response at study Day 169. Other joint-related efficacy endpoints measured during the study (ST and LT periods) were the proportion of subjects who had an ACR 50 and ACR 70 response; proportion of subjects with a HAQ response (improvement of at least 0.3 units from baseline in HAQ-Disability Index [DI]); proportion of subjects with a clinical response, defined as a reduction of at least 1.2 units from baseline in the Disease Activity Score-28 based on C-reactive protein (DAS28-CRP) score; mean changes from baseline in physical and mental component scores (PCS and MCS) of the SF-36; and mean change from baseline in bone erosions, bone edema, synovial volume, dactylitis and enthesitis as measured by MRI.

Skin-related efficacy endpoints included the proportion of subjects who achieved an IGA score of clear or almost clear; mean percent improvement from baseline in the target lesion score and the percentage of subjects with at least a 50% or 75% improvement in target lesion score (TL50, TL75); and proportion of subjects with baseline BSA ≥ 3% for psoriasis who achieved a 50% or 75% improvement in psoriasis as measured by the Psoriasis Area and Severity Index (PASI 50 and PASI 75).

Sample size

According to prior RA studies, the ACR 20 response rate was estimated to be 20% in the placebo. A total of 164 randomized subjects allocated evenly to the 4 treatment groups yielded 92% power to detect an absolute difference of 35% in ACR 20 response rate between the 30/10 mg/kg abatacept treatment group and the placebo. In addition, it yielded at least 84% power to detect the same difference in ACR 20 response rate between the 10/10 mg/kg abatacept group and the placebo using the sequential test procedure.

Randomisation

At the time of enrolment, each subject was assigned a unique sequential subject number for identification throughout the study via the Central Randomization System (Interactive Voice Randomization System [IVRS]).

The block size for randomization was 4. Randomization was stratified by the percentage of psoriasis-affected BSA (≥ 3% or < 3 %) at the time of the screening visit.

Blinding (masking)

In the ST period, the subjects and clinical investigational staff were blinded to treatment assignment. The pharmacist (or qualified drug preparation person) was unblinded to study medication and prepared the appropriate dose of active drug or placebo.

The LT period was open-label in design beginning with the first dose of study drug on Day 169.

Statistical methods

Efficacy analyses for the ST period were based on all randomized and treated subjects. For all the response rate comparisons between the treatment groups (placebo with each of the 3 abatacept regimens), Cochran-Mantel-Haenszel (CMH) Chi-square tests with randomization stratification were performed, unless otherwise noted. All comparisons of changes from baseline and construction of confidence intervals (CIs) for continuous measures were based on an analysis of covariance (ANCOVA) model that included treatment as the main factor and the baseline values as a covariate.

All subjects who prematurely discontinued the study after receiving study drug, regardless of reason, had missing ACR, IGA, HAQ, PASI response, and target lesion responses imputed as non-responders at all scheduled protocol visits subsequent to the point of discontinuation. Missing target lesion scores at Day 169 were imputed using a last observation carried forward (LOCF) approach.

No formal statistical testing was done on any data for the LT period. Analyses of safety, immunogenicity, and efficacy were descriptive in nature and based on as-observed data. All efficacy and safety analyses for the LT period were performed on the All Treated Subjects in the LT Period population, defined as subjects who received at least 1 infusion of abatacept in the LT period, and were presented by randomized treatment cohort in the ST period.

Results

Participant flow

ST period

A total of 191 subjects were enrolled in the study; of these, 170 were randomized. The primary reasons that enrolled subjects were not randomized were failure to meet study criteria (13/21) and withdrawal of consent (5/21). Of the 170 randomized and treated subjects, 147 subjects completed the 6-month ST 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%). Among the 23 subjects across all treatment groups who were discontinued from the ST period, there were no clinically relevant differences in the proportion of subjects discontinued for a specific reason among the 128 abatacept-treated and the 42 placebo-treated subjects (see Table 18).

Table 18 - Subject Disposition - Reasons for Discontinuation During Double-blind Period - All Randomized and Treated Subjects

	Number (%) of Subjects			
	Abatacept 30/10 N=43	Abatacept 10/10 N=40	Abatacept 3/3 N=45	Placebo N=42
Number Discontinued	6 (14.0)	6 (15.0)	2 (4.4)	9 (21.4)
Death	0	0	0	0
Adverse Event	1 (2.3)	2 (5.0)	1 (2.2)	3 (7.1)
Lack of Efficacy	3 (7.0)	4 (10.0)	0	3 (7.1)
Lost to Follow-up	0	0	0	0
Withdrawal of Consent	2 (4.7)	0	0	2 (4.8)
Subject no longer meets study criteria	0	0	0	1 (2.4)
Poor/Non-compliance	0	0	0	0
Pregnancy	0	0	1 (2.2)	0
Administrative reason by sponsor	0	0	0	0
Other	0	0	0	0
Number Completed Double-Blind Period	37 (86.0)	34 (85.0)	43 (95.6)	33 (78.6)

Open-label period

Each of the 147 treated subjects who completed the ST period entered the LT period and received at least 1 infusion of open-label abatacept (All Treated Subjects in LT Period population). Approximately one-half of the 147 subjects treated in the LT period were discontinued for administrative reasons related to termination of the study by BMS (n = 76, 51.7%). Lack of efficacy (34.0%) was the second most common reason for discontinuation during the LT period. Four subjects (2.7%) were discontinued from the LT period due to an AE(s) (2.7%). The proportion of subjects who were discontinued due to study termination or lack of efficacy did not differ as a function of randomized treatment in the ST period (see Table 19).

Table 19 - Subject Disposition - Reasons for Discontinuation During the Long-term Period - All Treated Subjects in LT Period

	Number (%) of Subjects				
	Abatacept 30/10 (N=37)	Abatacept 10/10 (N=34)	Abatacept 3/3 (N=43)	Placebo (N=33)	Total (N=147)
Number Discontinued	37 (100.0)	34 (100.0)	43 (100.0)	33 (100.0)	147 (100.0)
Death	0	0	0	0	0
Adverse Event	2 (5.4)	1 (2.9)	0	1 (3.0)	4 (2.7)
Lack of Efficacy	14 (37.8)	10 (29.4)	14 (32.6)	12 (36.4)	50 (34.0)
Lost to Follow-up	1 (2.7)	2 (5.9)	0	0	3 (2.0)
Withdrawal of Consent	2 (5.4)	2 (5.9)	0	0	4 (2.7)
Subject no longer meets study criteria	0	1 (2.9)	0	0	1 (0.7)
Poor/Non-compliance	0	1 (2.9)	1 (2.3)	0	2 (1.4)
Pregnancy	0	0	0	0	0
Administrative reason by sponsor	17 (45.9)	15 (44.1)	26 (60.5)	18 (54.5)	76 (51.7)
Other	1 (2.7)	2 (5.9)	2 (4.7)	2 (6.1)	7 (4.8)

Recruitment

Study Initiation Date: 27-Nov-2007; Short-term Period Completion Date: 29-Dec-2008; Long-term Period Initiation Date: 29-May-2008; Long-term Period Termination Date: 18-Jan-2011

Conduct of the study

Protocol deviations

A total of 7 subjects had a relevant protocol deviation, including 6 (13.3%) in the abatacept 3/3 mg/kg group and 1 (2.4%) in the placebo group. No subject in the abatacept 10/10 or 30/10 mg/kg groups had a relevant protocol deviation. For 4 of the 6 subjects in the abatacept 3/3 mg/kg group, the relevant deviation consisted of not having a stable MTX dose for at least 28 days prior to screening.

Changes in the Conduct of the Study

There were 4 amendments to the original protocol and 2 administrative letters. Study IM101158 was terminated by BMS after completion of the ST period, and notification of the intent to terminate this study

was communicated to all sites participating in the LT period in a letter dated 31-Aug-2010. Sites were instructed to discontinue treatment in all active subjects as of Jan-2011.

Changes to the planned analysis

The planned prediction of PK data for the 3 abatacept treatment groups using population PK methodology was not performed as it was determined that this type of analysis would not provide any relevant information over the observed summary of Cmin data. Samples collected for the pharmacogenetic analysis were not analyzed.

The ACR 20 and ACR 50 response rates at Day 169 were summarized by treatment group using point estimates and 95% CI for subjects who had and had not previously been exposed to TNF inhibitors. These post hoc analyses were added in order to determine the relative efficacy in each of these subgroups.

Baseline data

A total of 91 males (53.5%) and 79 females (46.5%), with a mean age of 51.3 years (range: 26 to 82 years) participated in the study. Subjects were predominately white (97.6%), with a mean body weight of 89.7 kg (range 49 to 149.7 kg). The majority of subjects (57.1%) were enrolled at sites in North America. The mean IGA score at baseline (2.5) indicated mild to moderate skin disease, while the mean tender and swollen joint counts suggested moderate arthritis activity at baseline (22.2 and 10.9, respectively).

The majority of subjects in each treatment group 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 enrollment (range: 57.1% to 60.0%) (see Table 20). Nonsteroidal anti-inflammatory drugs were the second most common anti-rheumatic drug class used at enrolment (range: 54.8% to 71.1%). A total of 63 of the 170 randomized and treated subjects (37.0%) had a history of anti-TNF biologic use, and previous use of these agents was more common for subjects randomized to the abatacept 30/10 mg/kg group (51.2%) and ranged from 28.6 to 35.6% for the other 3 treatment groups. No subject was receiving biologic therapy at enrollment into the study.

While between 21.4% and 27.5% of subjects had a history of DMARD therapy (other than MTX), only a small minority of randomized and treated subjects were receiving non-MTX DMARD therapy at the time of study enrollment (5.0% to 8.9% across treatment groups). Between approximately one-fifth and one-quarter of subjects in each treatment group (19.0% to 27.5%) were receiving corticosteroids at enrollment. The mean oral steroid dose was similar across the 4 treatment groups. With respect to concomitant therapy, the number of subjects who used concomitant corticosteroids was slightly higher than that reported at Day 1.

Table 20 - Antirheumatic Medication Summary at Screening/Enrollment (ST Period) - All Randomized and Treated Subjects

	Number (%) of Subjects							
	Abatacept 30/10 N=43		Abatacept 10/10 N=40		Abatacept 3/3 N=45		Placebo N=42	
Total Subjects on CONMEDs	40	(93.0)	36	(90.0)	41	(91.1)	33	(78.6)
Methotrexate	25	(58.1)	24	(60.0)	27	(60.0)	24	(57.1)
Corticosteroids (oral and/or injectable)	10	(23.3)	11	(27.5)	12	(26.7)	8	(19.0)
NSAIDS	25	(58.1)	28	(70.0)	32	(71.1)	23	(54.8)
Other DMARDS	3	(7.0)	2	(5.0)	4	(8.9)	3	(7.1)
Azathioprine	1	(2.3)	0		0		0	
Hydroxychloroquine	1	(2.3)	0		2	(4.4)	0	
Leflunomide	0		0		1	(2.2)	1	(2.4)
Sulfasalazine	1	(2.3)	2	(5.0)	1	(2.2)	2	(4.8)
Mean Oral Dose Corticosteroids (SD)	1.7	(3.67)	1.6	(3.86)	1.6	(3.06)	1.3	(3.09)

Numbers analysed

All of the randomized and treated subjects received double-blind study medication in the ST period according to the randomization schedule. Thus, the All Treated and the ITT (also called All Randomized and Treated Subjects) analysis populations were identical and included a total of 170 subjects (43 in abatacept 30/10 mg/kg group, 40 in abatacept 10/10 mg/kg group, 45 in abatacept 3/3 mg/kg group, and 42 in placebo group).

The 147 subjects who completed the ST period and received at least 1 infusion of open-label abatacept in the LT period comprise the All Treated Subjects in LT Period population.

The All Abatacept-treated Subjects population was composed of the 161 subjects who received at least 1 infusion of abatacept in the ST and/or LT period (includes 33 subjects who received abatacept only in LT period [i.e., received placebo in ST period]).

Outcomes and estimation

Primary Efficacy Endpoint

Overall, the portion of PsA subjects with ACR 20 response rate at Day 169 (primary efficacy endpoint) was similar for abatacept 30/10 and abatacept 10/10 treatment groups, and the ACR 20 response rate for both of these abatacept groups was significantly higher in comparison to the placebo group (see Table 21). The response rate for abatacept 3/3 treatment group was not significantly higher in comparison to the placebo group.

Table 21 - Proportion of Subjects with ACR 20 Response Rate at Day 169 – All Randomized and Treated Subjects

	Abatacept 30/10 N = 43	Abatacept 10/10 N = 40	Abatacept 3/3 N = 45	Placebo N = 42
Number of responders (%)	18 (41.9%)	19 (47.5%)	15 (33.5%)	8 (19.0%)
95% CI	(27.1, 56.6)	(32.0, 63.0)	(19.6, 47.1)	(7.2, 30.9)
Estimate of Diff. (95% CI)	22.9 (4.0, 41.8)	28.7 (9.4, 48.0)	14.6 (-3.5, 32.6)	N/A
p-value[a]	0.022	0.006	0.121	N/A

Estimate of difference and p-value are based on Cochran-Mantel-Haenszel method (CMH) with stratification of baseline body surface area (BSA) affected by psoriasis.

N/A = not applicable.

[a] Probability for testing the difference between abatacept and placebo.

Secondary Efficacy Endpoints

The proportion of subjects with IGA response of clear or almost clear at Day 169 was highest for abatacept 3/3 mg/kg group in comparison to similar lower rates for the abatacept 30/10 mg/kg, abatacept 10/10 mg/kg, and placebo groups (see Table 22).

Table 22 - Proportion of Subjects with IGA Response at Day 169 – All Randomized and Treated Subjects

	Abatacept 30/10 N = 43	Abatacept 10/10 N = 40	Abatacept 3/3 N = 45	Placebo N = 42
Number of responders (%)	9 (20.9%)	10 (25.0%)	17 (37.8%)	11 (26.2%)
95% CI	(8.8, 33.1)	(11.6, 38.4)	(23.6, 51.9)	(12.9, 39.5)
Estimate of Diff. (95% CI)	-6.0 (-23.0, 11.0)	-0.5 (-18.0, 17.1)	10.4 (-7.6, 28.5)	N/A

IGA refers to Investigator Global Assessment. Response is assessment of 'clear' or 'almost clear'.
Source: Annex A, Table S.5.2.1.

The adjusted mean percentage improvement from baseline at Day 169 (LOCF) in the target lesion score was notably higher in each of the 3 abatacept treatment groups compared with the placebo group, with the largest adjusted difference from placebo observed for the abatacept 3/3 mg/kg group relative to the abatacept 30/10 mg/kg (18.77%) and abatacept 10/10 mg/kg (22.34%) groups (see Table 23).

Table 23 - Adjusted Mean Percent Improvement from Baseline in Target Lesion Score at Day 169 (LOCF) – All Randomized and Treated Subjects

		Abatacept 30/10 N = 43	Abatacept 10/10 N = 40	Abatacept 3/3 N = 45	Placebo N = 42
TL	n	43	40	45	41
	Baseline Mean (SD)	6.60 (2.82)	6.00 (2.43)	5.49 (2.66)	6.34 (2.68)
	Post-baseline Mean (SD)	4.88 (2.99)	4.55 (3.08)	3.82 (3.08)	5.32 (2.88)
	Adj. Mean % Improvement from Bsln (SE)	19.39 (9.16)	22.96 (9.46)	31.11 (8.98)	0.63 (9.35)
	Adj. Diff. from Placebo (95% CI)	18.77 (-7.02, 44.56)	22.34 (-3.93, 48.60)	30.48 (4.82, 56.15)	N/A

Improvements of > 3 points in the SF-36 PCS and MCS scores are considered clinically relevant in patients with RA. Subjects treated with abatacept (all 3 treatment groups) demonstrated greater improvement at Day 169 in the physical component of SF-36 in comparison to subjects treated with placebo. The 95% CIs for each of the adjusted differences from placebo in the abatacept groups did not contain zero. Although the adjusted mean improvements from baseline at Day 169 in the mental component of the SF-36 was larger for all 3 abatacept groups compared with placebo, the adjusted differences from placebo were modest, and all 95% CIs for the adjusted differences contained zero (see Table 24).

Table 24 - Adjusted Mean Change from Baseline at Day 169 (LOCF) in Physical and Mental Component Scores of SF-36 - All Randomized and Treated Subjects

		Abatacept 30/10 N = 43	Abatacept 10/10 N = 40	Abatacept 3/3 N = 45	Placebo N = 42
PCS	n	42	40	43	41
	Baseline Mean (SD)	37.76 (12.73)	32.12 (13.42)	37.53 (16.03)	37.34 (15.81)
	Post-baseline Mean (SD)	44.73 (15.08)	42.29 (17.30)	43.56 (16.84)	37.25 (16.64)
	Adjusted Mean Change from Baseline (SE)	7.30 (1.85)	9.27 (1.91)	6.32 (1.82)	0.15 (1.87)
	Adjusted Diff. from Placebo (95% CI)	7.15(1.97, 12.33)	9.12(3.83, 14.41)	6.17(1.01, 11.32)	N/A
MCS	n	42	40	43	41
	Baseline Mean (SD)	66.81 (20.38)	63.87 (23.42)	65.41 (20.36)	63.77 (20.19)
	Post-baseline Mean (SD)	70.59 (20.08)	68.73 (19.25)	68.41 (21.70)	66.66 (20.10)
	Adjusted Mean Change from Baseline (SE)	4.50 (2.45)	4.42 (2.50)	3.16 (2.41)	2.41 (2.47)
	Adjusted Diff. from Placebo (95% CI)	2.08(-4.79, 8.96)	2.01(-4.94, 8.95)	0.75(-6.08, 7.58)	N/A

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 HAQ-DI score, was higher for all 3 abatacept groups than for the placebo group (see Table 25).

Table 25 - Proportion of Subjects with HAQ Response at Day 169: All Randomized and Treated Subjects

		Abatacept 30/10 N = 43	Abatacept 10/10 N = 40	Abatacept 3/3 N = 45	Placebo N = 42
Day 169	Number of responders (%)	15 (34.9%)	18 (45.0%)	16 (35.6%)	8 (19.0%)
	95% CI	(20.6, 49.1)	(29.6, 60.4)	(21.6, 49.5)	(7.2, 30.9)
	Estimate of Diff. (95% CI)	16.0 (-2.5, 34.5)	26.1 (6.8, 45.5)	16.6 (-1.8, 34.9)	N/A

HAQ response is defined as an improvement of at least 0.3 unit from baseline in the HAQ Disability Index.
Estimate of Difference and 95% CIs are calculated based on Cochran-Mantel-Haenszel method (CMH) with stratification of baseline body surface area (BSA) affected by psoriasis.
N/A = not applicable.

Selected exploratory efficacy endpoints (Please see also section "Analysis performed across trials")

Changes from baseline (mean and median) in MRI results for erosion, edema, synovitis, dactylitis, and enthesitis at Day 169 are summarized by treatment group in Table 26. Mean baseline MRI scores were consistently larger for the abatacept 10/10 mg/kg group.

Mean changes from baseline in erosion scores at Day 169 were smaller in all 3 abatacept groups compared with the placebo group. Mean reductions from baseline at Day 169 in synovitis, edema, and enthesitis, as assessed by MRI, were also observed in all 3 abatacept groups compared with mean increases in the placebo group.

Table 26 - Changes from Baseline in Magnetic Resonance Images Results at Day 169 - All Randomized and Treated Subjects

		Abatacept 30/10 N = 43	Abatacept 10/10 N = 40	Abatacept 3/3 N = 45	Placebo N = 42
Erosion	n	30	26	28	26
	Baseline Mean (SD)	3.62 (4.26)	7.87 (14.91)	3.45 (4.73)	2.85 (4.36)
	Baseline Median (Range)	1.50 (0.00, 15.00)	3.00 (0.00, 77.00)	1.75 (0.00, 16.50)	1.00 (0.00, 19.00)
	Mean Change from Bsln (SD)	0.30 (3.49)	-0.60 (4.23)	0.54 (2.37)	1.48 (7.37)
	Median Change (25%, 75%)	0.00 (-1.00, 1.00)	-0.50 (-2.00, 2.00)	0.00 (-0.50, 1.25)	0.00 (-0.50, 1.00)
Edema	n	30	26	28	26
	Baseline Mean (SD)	2.23 (2.49)	4.19 (3.62)	2.38 (3.20)	1.65 (2.03)
	Baseline Median (Range)	1.50 (0.00, 8.50)	4.00 (0.00, 13.50)	1.00 (0.00, 11.50)	0.75 (0.00, 7.50)
	Mean Change from Bsln (SD)	-0.47 (1.91)	-1.12 (2.55)	-0.32 (1.72)	0.44 (3.33)
	Median Change (25%, 75%)	0.00 (-1.00, 0.00)	-1.00 (-3.50, 0.50)	0.00 (-1.00, 0.50)	0.00 (-0.50, 1.00)
Synovitis	n	30	26	28	26
	Baseline Mean (SD)	8.30 (4.29)	10.06 (4.54)	8.52 (4.63)	6.88 (3.76)
	Baseline Median (Range)	9.00 (1.50, 15.50)	9.00 (3.50, 24.00)	8.75 (1.50, 23.50)	5.50 (1.50, 15.50)
	Mean Change from Bsln (SD)	-0.75 (3.08)	-1.40 (2.99)	-0.23 (2.85)	0.81 (4.33)
	Median Change (25%, 75%)	-0.50 (-2.00, 1.00)	-1.25 (-3.50, 0.50)	0.00 (-1.25, 1.50)	1.00 (-3.00, 3.00)
Dactylitis	n	30	26	28	26
	Baseline Mean (SD)	0.25 (0.60)	0.58 (0.96)	0.11 (0.31)	0.23 (0.45)
	Baseline Median (Range)	0.00 (0.00, 2.50)	0.00 (0.00, 3.50)	0.00 (0.00, 1.50)	0.00 (0.00, 1.50)
	Mean Change from Bsln (SD)	-0.08 (0.46)	-0.27 (0.70)	-0.02 (0.25)	-0.10 (0.51)
	Median Change (25%, 75%)	0.00 (0.00, 0.00)	0.00 (-0.50, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Enthesitis	n	30	26	28	26
	Baseline Mean (SD)	1.12 (1.17)	1.83 (1.97)	0.93 (1.33)	0.81 (0.84)
	Baseline Median (Range)	0.75 (0.00, 4.00)	1.50 (0.00, 9.00)	0.50 (0.00, 5.00)	0.75 (0.00, 2.50)
	Mean Change from Bsln (SD)	-0.28 (1.07)	-1.04 (1.51)	-0.14 (0.88)	0.04 (1.29)
	Median Change (25%, 75%)	0.00 (-0.50, 0.00)	-0.75 (-1.50, 0.00)	0.00 (-1.00, 0.25)	0.00 (-1.00, 0.50)

n is the number of subjects with both baseline and post-baseline measurements.
Dactylitis and Enthesitis scores are based on the MRI assessments.
Change from Baseline = Post-baseline - Baseline value.
Exc. Infla. and Intd. Edema refer to Extracapsular Inflammation and Intratendinous Edema/Enhancement, respectively.
'Median Change' refers to Median Change from Baseline.
Edema/Enhance = Edema/Enhancement at Insertion.

Exploratory analyses of the ACR 20 and ACR 50 response rates at Day 169 as a function of prior exposure to a TNFα blocker(s) were conducted. Table 27 presents the results of these analyses. Results showed separation from placebo for all 3 abatacept groups among subjects who had prior exposure to an anti-TNFα as well as for those who were anti-TNFα naïve.

Table 27 - ACR 20 and ACR 50 Response Rates at Day 169 by TNF Use - All Randomized and Treated Subjects

ACR 20 Response at Day 169

		Abatacept 30/10 (N = 21)	Abatacept 10/10 (N = 27)	Abatacept 3/3 (N = 29)	Placebo (N = 30)
TNF Use: No					
ACR20	Number of subjects (%)	10 (47.6%)	15 (55.6%)	10 (34.5%)	6 (20.0%)
	95% CI	(26.3, 69.0)	(36.8, 74.3)	(17.2, 51.8)	(5.7, 34.3)
TNF Use: Yes					
		Abatacept 30/10 (N = 22)	Abatacept 10/10 (N = 13)	Abatacept 3/3 (N = 16)	Placebo (N = 12)
ACR20	Number of subjects (%)	8 (36.4%)	4 (30.8%)	5 (31.3%)	2 (16.7%)
	95% CI	(16.3, 56.5)	(5.7, 55.9)	(8.5, 54.0)	(-4.4, 37.8)

ACR 50 Response at Day 169

		Abatacept 30/10 (N = 21)	Abatacept 10/10 (N = 27)	Abatacept 3/3 (N = 29)	Placebo (N = 30)
TNF Use: No					
ACR50	Number of subjects (%)	4 (19.0%)	8 (29.6%)	5 (17.2%)	0
	95% CI	(2.3, 35.8)	(12.4, 46.9)	(3.5, 31.0)	(0.0, 0.0)
TNF Use: Yes					
		Abatacept 30/10 (N = 22)	Abatacept 10/10 (N = 13)	Abatacept 3/3 (N = 16)	Placebo (N = 12)
ACR50	Number of subjects (%)	5 (22.7%)	2 (15.4%)	2 (12.5%)	1 (8.3%)
	95% CI	(5.2, 40.2)	(0.0, 35.0)	(0.0, 28.7)	(0.0, 24.0)

LT period / Secondary Efficacy Endpoints

The improvements in ACR 20, ACR 50, and ACR 70 rates that were evident in the abatacept 30/10 and 10/10 mg/kg groups at the end of the ST period were at least maintained during continued treatment with abatacept 10 mg/kg in the LT period for up to Day 897 (~ Month 30 of study). ACR 20 rates at Days 169 (end of ST period), 365, and 729 were 48.6% (18/37), 50% (17/34), and 81.0% (17/21), respectively, in the ST abatacept 30/10 mg/kg group and 55.9% (19/34), 62.1% (18/29), and 66.7% (12/18), respectively, in the ST abatacept 10/10 mg/kg group.

ACR 20, ACR 50, and ACR 70 rates for subjects in the ST 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 LT period. ACR 20 rates at Days 169 (end of ST period), 365, and 729 were 24.2% (8/33), 46.9% (15/32), and 72.2% (13/18), respectively, in the ST placebo cohort and 34.9% (15/43), 61.1% (22/36), and 65.4% (17/26), respectively, in the ST abatacept 3/3 mg/kg cohort.

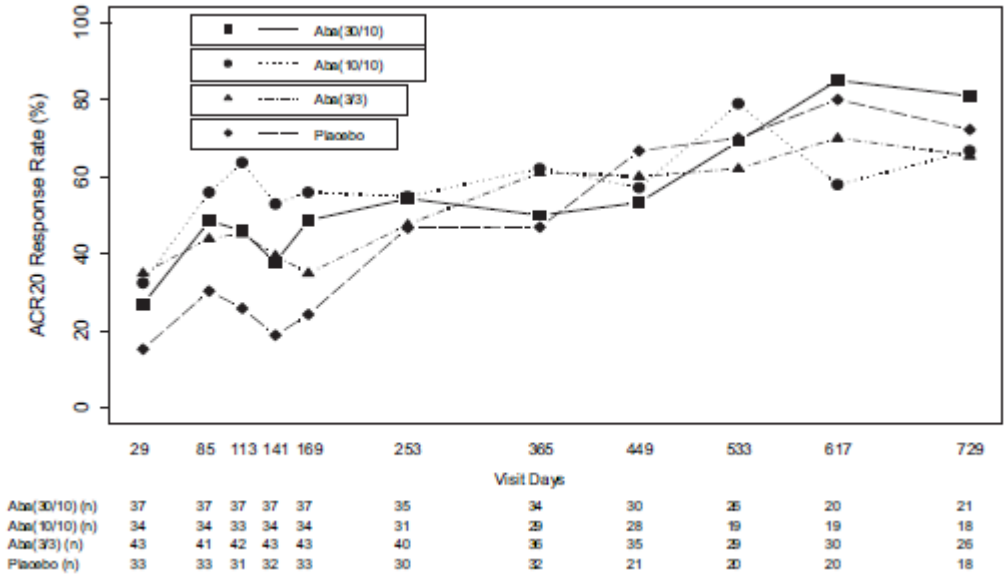


Figure 19 - ACR 20 Response Rates over Time by Randomized Treatment Assignment in ST Period - All Treated Subjects in LT Period

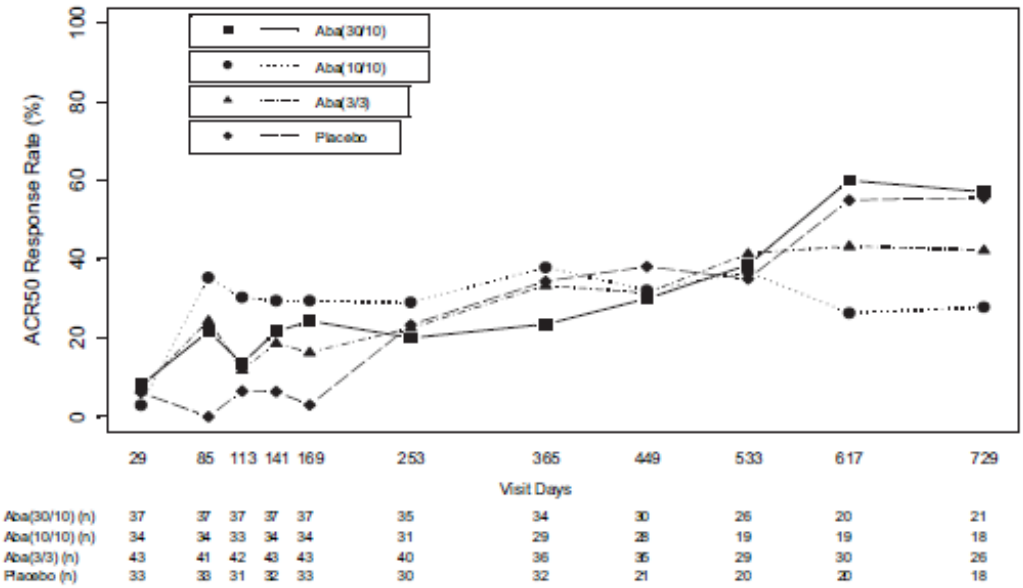


Figure 20 - ACR 50 Response Rates over Time by Randomized Treatment Assignment in ST Period - All Treated Subjects in LT Period

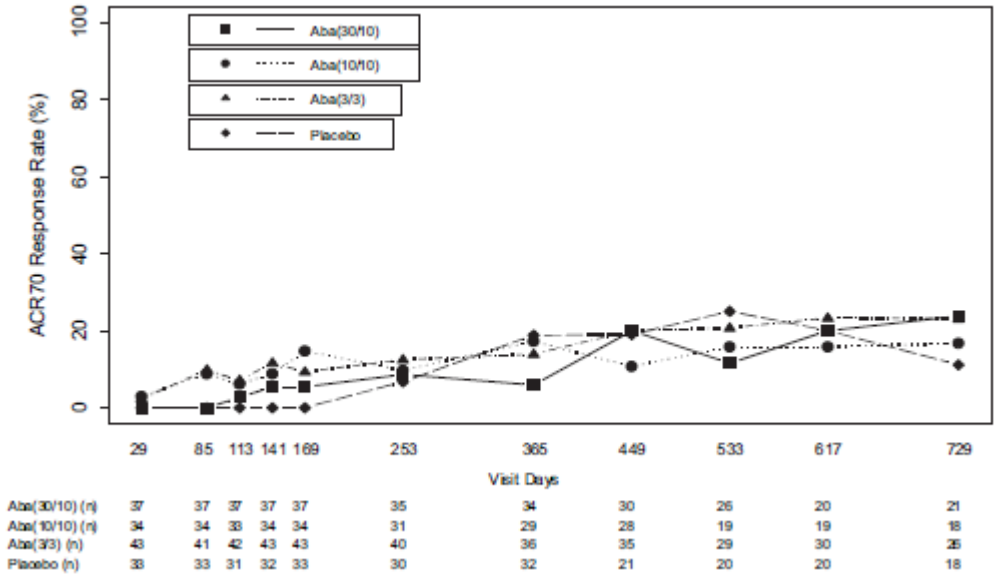


Figure 21 - ACR 70 Response Rates over Time by Randomized Treatment Assignment in ST Period - All Treated Subjects in LT Period

IGA response rate at Day 169 and at Days 365 and 729 of the LT period were:

- 25.0% (9/36), 43.3% (13/30), and 50.0% (10/20), respectively, in the ST abatacept 30/10 mg/kg cohort
- 29.4% (10/34), 34.5% (10/29), 41.2% (7/17), respectively, in the ST abatacept 10/10 mg/kg cohort
- 39.5% (17/43), 55.9% (19/34), 61.5% (16/26), respectively, in the ST abatacept 3/3 mg/kg cohort, and
- 33.3% (11/33), 43.5% (10/23), and 44.4% (8/18), respectively in the ST placebo cohort.

Following initiation of treatment with abatacept 10 mg/kg in the LT period, subjects who had been treated with placebo in the ST period showed larger (i.e., improvements) mean percentage changes from baseline in the target lesion score, with values of 33.82% (± SE of 7.52) at Day 365 and 34.41% (± 8.98) at Day 729 compared with 14.80% at Day 169. While the mean percentage change from baseline in target lesion score continued to improve in the abatacept 10/10 mg/kg and was maintained in the abatacept 30/10 mg/kg groups, it worsened in the abatacept 3/3 mg/kg group.

The mean improvements at Day 169 in the physical component of SF-36 observed in the 3 abatacept groups were at least maintained during treatment with abatacept 10 mg/kg in the LT period. The mean (SE) improvement in the SF-36 PCS score at Days 169, 365, and 729 for the All Treated Subjects in LT Period by ST randomized treatment cohort were:

- 2.91 (1.15), 1.73 (1.10),and 5.59 (1.43), respectively, in the abatacept 30/10 mg/kg cohort
- 6.07 (1.51), 7.59 (1.36), 7.97 (2.00), respectively, in the abatacept 10/10 mg/kg cohort
- 1.88 (1.27), 4.86 (1.67), 6.74 (1.95), respectively, in the abatacept 3/3 mg/kg cohort
- -1.60 (1.16), 3.59 (1.19), and 4.45 (1.14), respectively, in the placebo cohort.

The HAQ response rates at Days 169 (end of ST period), 365, and 729 for the ST randomized treatment cohorts were:

- 40.5% (15/37), 40.0% (12/30), and 45.0% (9/20), respectively, in the abatacept 30/10 mg/kg cohort
- 52.9% (18/34), 57.1% (16/28), and 64.7% (11/17), respectively, in the abatacept 10/10 mg/kg cohort
- 38.1% (16/42), 53.1% (17/32), and 50.0% (13/26), respectively, in the abatacept 3/3 mg/kg cohort,

24.2% (8/33), 52.2% (12/23), and 55.6% (10/18), respectively, in the placebo cohort.

2.4.2. Main studies

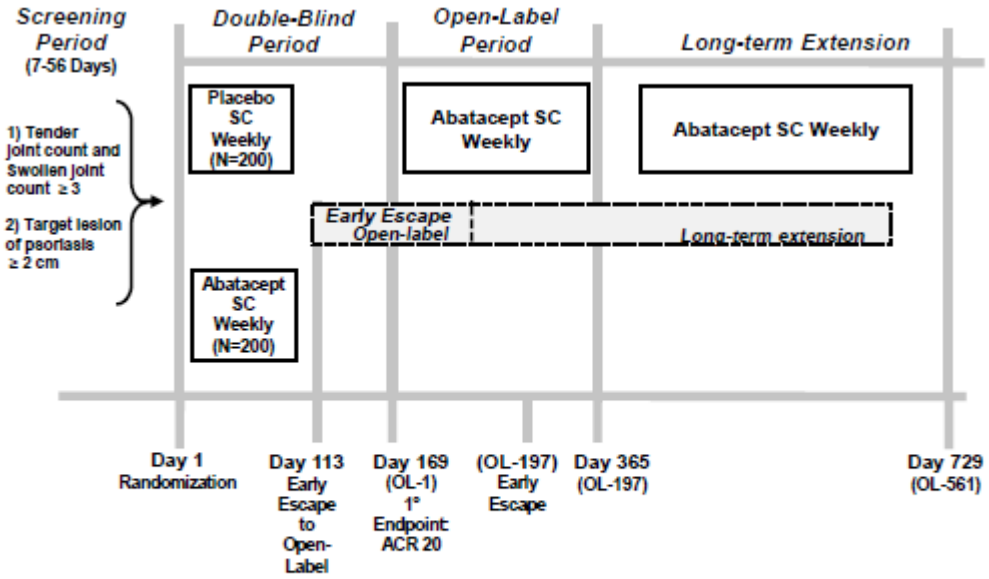
A Phase 3 Randomized Placebo Controlled Study to Evaluate the Efficacy and Safety of Abatacept Subcutaneous Injection in Adults with Active Psoriatic Arthritis (Study IM101332)

Methods

This was a 24-week (169 days), Phase 3, randomized, double-blind, placebo controlled, multicenter study, followed by a 28-week (196 days) Open label Period and a 52-week Long Term Extension in subjects with 1) active PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR) and 2) active psoriasis defined as having at least one lesion of psoriasis (at least ≥ 2 cm in diameter).

Subjects were randomized in a 1:1 ratio to 125 mg SC weekly of abatacept or placebo, including subjects with and without prior TNFi exposure. Randomization was stratified globally by current methotrexate (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% BSA psoriatic skin involvement were planned to be randomized.

On Day 113, subjects who had not achieved a ≥ 20% improvement from baseline (Day 1) in their swollen and tender joint counts were considered treatment failures, removed from their blinded treatment arm, and transitioned to the Early Escape arm in which they received open-label weekly SC abatacept 125 mg. At Day 169, all subjects transitioned to the Open-label Period and received abatacept 125 mg SC weekly. At the end of the OL Period, subjects had the option of entering a 1-year, Long-term Extension Period during which only safety data was collected (see Figure 22).



OL = Open-label.
Note: The study included a 6-month post-dose follow-up period (28, 84, and 168 days post treatment) when subjects were no longer receiving study medication; safety and immunogenicity assessments were performed for this period.
Source: Figure 3.1-1 of the IM101332 CSR.[4]

Figure 22 - Study Design - Study IM101332

Study participants

Key inclusion criteria:

- Subjects have a diagnosis of PsA by CASPAR.
- Subjects have at least one confirmed ≥ 2 cm target lesion of plaque psoriasis in a region of the body that can be evaluated excluding the axilla, genitals, groin, palms, and soles at screening and randomization/Day 1.
- Subjects must have had an inadequate response or intolerance to at least one non-biologic DMARD.
- Subjects may have been exposed to TNFi therapy. Subjects may have discontinued for any reason (inadequate response, intolerance or other).
- Subjects have active disease as shown by a minimum of ≥ 3 swollen joints and ≥ 3 tender joints (66/68 joint counts) at screening and randomization/Day 1 (prior to study drug administration). At least one of the swollen joints must be in the digit of the hand or foot.
- If currently on a non-biologic DMARDs [methotrexate (maximum of 25 mg weekly), leflunomide, sulfasalazine, or hydroxychloroquine], the medication must have been used for at least 3 months with a stable dose for at least 28 days prior to randomization (Day 1).
- NSAID doses must be stable for at least 14 days before randomization (Day 1) and consistent with labeling recommendations.
- If using oral corticosteroids (≤ 10 mg/day prednisone equivalent), dose must be stable ≥ 14 days before randomization (Day 1).

- Subjects may enroll on systemic retinoids (eg, acitretin) provided the subject has used the medication for at least 3 months with a stable dose at least 4 weeks prior to randomization (Day 1).
- Permitted topical therapy for plaque psoriasis must have been stable for ≥ 14 days prior to randomization (Day 1).
- Subject Re-enrollment: This study permitted the re-enrollment of a subject who had discontinued the study as a pre-treatment failure (ie subject had not been randomized). If re-enrolled, the subject was to be re-consented.
- Men and women, at least 18 years of age.
- Women of childbearing potential (WOCBP) must use method(s) of contraception based on guidelines described in the protocol.

Key exclusion criteria:

- Subjects with active systemic inflammatory condition other than PsA (eg, systemic lupus erythematosus).
- Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, psychiatric, cardiac, neurological, or cerebral disease including severe and uncontrolled infections, such as sepsis and opportunistic infections.
- Concomitant medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
- Female subjects who had a breast cancer screening procedure that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations.
- Subjects with a history of cancer within the last 5 years (other than non-melanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to dosing. Subjects with carcinoma in situ, treated with definitive surgical intervention prior to study enrollment are allowed.
- Subjects with a history of (within 12 months of signing informed consent), or known current problems with drug or alcohol abuse history or known cirrhosis including alcoholic cirrhosis.
- Subjects with any bacterial infection within the last 60 days prior to screening (enrollment), unless treated and resolved with antibiotics, or any chronic bacterial infection (such as chronic pyelonephritis, osteomyelitis and bronchiectasis).
- Subjects at risk for TB. Specifically, subjects with current clinical, radiographic or laboratory evidence of active TB.
- Subjects with herpes zoster that resolved less than 2 months prior to enrollment.
- Subjects with evidence (as measured by the investigator) of active or latent bacterial, active viral, or serious latent viral infections at the time of enrollment, including subjects with evidence of HIV infection.
- Subjects with guttate, pustular, or erythrodermic psoriasis.
- Subjects who have a history of systemic fungal infections (such as histoplasmosis, blastoplasmosis, or coccidioides).

- Subjects who fulfill ACR Functional Class 4.
- Subjects who have had prior exposure to abatacept (CTLA4-Ig) or other CTLA4 therapies.
- Subjects who have been exposed to any investigational drug within 4 weeks or 5 halflives prior to randomization (Day 1), whichever is longer
- Subjects who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines. (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).
- Subjects who are not currently treated with a non-biologic DMARD and have clinical or radiographic evidence of arthritis mutilans (eg, digital telescoping or "pencil-in-cup" radiographic changes).
- Subjects who have discontinued a non-biologic DMARD or systemic retinoid within four weeks or five half-lives prior to randomization (Day 1) whichever is longer.
- Subjects who have discontinued oral corticosteroids within 14 days prior to randomization (Day 1).
- Subjects who have received an IM, IV or IA administration of a corticosteroid ≤ 28 days prior to randomization (Day 1).
- Subjects who have discontinued oral NSAIDs within 14 days prior to randomization (Day 1).
- Subjects who have failed more than 2 TNFi agents due to inefficacy with inefficacy defined as inadequate response after 3 months of treatment at a therapeutic dose. NOTE: There is no limit on the total number of TNFi to which the subject has been exposed.
- Subjects who have received TNFi therapy within 4 weeks for etanercept or within 8 weeks for adalimumab, certolizumab, infliximab, or golimumab prior to randomization (Day 1).
- Prior use of rituximab ≤6 months ago; if after > 6 months has elapsed since use, must have documented reconstitution of total peripheral B cell counts to a level within normal laboratory range.
- Subjects who have been treated with apremilast within 4 weeks, ustekinumab within 20 weeks, or briakinumab within 8 weeks prior to randomization (Day 1).
- Use of any of the following within 28 days or five half-lives whichever is longer prior to randomization (Day 1): azathioprine, cyclosporine A, oral tacrolimus, mycophenolate mofetil, hydroxyurea, fumaric acid esters, paclitaxel, 6 thioguanine, 6 mercatopurine, or tofacitinib.
- Treatment with the following topical therapies within 14 days prior to randomization (Day 1): calcineurin inhibitors (tacrolimus and pimecrolimus), topical vitamin D analogs (eg, calcipotriene, calcitriol, tacalcitol), topical retinoids (eg, tazorotene), shampoo containing corticosteroids, topical tar and salicylic acid (except on the scalp), or medium to high potency corticosteroids (potency great than or equal to triamcinolone 0.1%).
- Hepatitis B surface antigen-positive subjects with detectable hepatitis B viral DNA or Hepatitis B core antibody positive subjects and with detectable hepatitis B viral DNA; Hepatitis C antibody-with detectable hepatitis C viral RNA; Hemoglobin < 8.5 g/dl; White Blood Count (WBC) < 3,000/mm3 (3 x 109/L); Platelets < 100,000/mm3 (100 x 109/L); Any laboratory test results

that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.

Treatments

During the first 6 months (blinded period), subjects received either abatacept 125 mg SC or placebo SC once per week according to the dosing schedule.

On Day 113, subjects who did not achieve a ≥ 20% improvement from baseline in their swollen and tender joint counts were considered treatment failures and removed from their blinded treatment arm and transitioned to "Early Escape" treatment with open-label weekly abatacept 125 mg SC. At Day 169, all subjects received abatacept 125 mg SC weekly.

Objectives

Primary Objective

- To compare the efficacy of abatacept to placebo as assessed by the ACR 20 response at Day 169.

Secondary Objectives

Key Secondary Objectives

- To compare the efficacy of abatacept to placebo as assessed by the HAQ response at Day 169
- To compare the efficacy of abatacept to placebo in the subset of subjects who have never been exposed to TNFi therapy, as assessed by the ACR 20 response at Day 169
- To compare the efficacy of abatacept to placebo in the subset of subjects who have previously taken TNFi therapy, as assessed by the ACR 20 response at Day 169
- To compare the efficacy of abatacept to placebo as assessed by the proportion of subjects who do not show progression of x-rays (using the PsA modified Sharp/van der Heidje score [SHS]) from baseline to Day 169

Other Secondary Objectives

- To compare the proportion of subjects achieving at least 50% improvement from baseline in psoriasis, as assessed by the PASI skin score between the two treatment groups at Day 169
- To assess the efficacy of abatacept to placebo as measured by the proportion of subjects achieving ACR 50 and ACR 70 response at Day 169
- To determine the improvement in the physical and mental function subscales of the SF-36, at Day 169
- To determine the proportion of subjects with at least one positive immunogenicity response up to Day 169
- To assess safety by the proportion of subjects with adverse events (all AEs, deaths, SAEs, and AEs leading to discontinuation) and the proportion of subjects with laboratory marked abnormalities up to Day 169

Exploratory Objectives

- To determine the proportion of ACR 20, ACR 50, ACR 70 and HAQ responders at Day 365 (Open-label Day 197)
- To determine the mean change from baseline in total PsA modified SHS score at Day 169 and Day 365 (Open-label Day 197).
- To determine the proportion of subjects who do not show progression of x-rays between Day169 and Day 365 (Open-label Day 197)
- To determine the proportion of subjects with improvement in psoriasis skin involvement as assessed by the PASI, the target lesion score, and the DLQI at Day 169 and Day 365 (Open-label Day 197)
- To determine the change from baseline in physical and mental functions at Day 365 (Open-label Day 197) as assessed by the SF-36
- To determine the proportion of subjects with low disease activity at Day 169 and Day 365 (Open-label Day 197) as assessed by the MDA and the DAS 28-CRP (remission and low disease activity)
- To determine the proportion of subjects responding based on composite measures of disease activity, including the modified CPDAI and PASDAS, at Day 169 and Day 365 (Open-label Day 197)
- To determine the change from baseline in spinal symptoms, enthesitis, dactylitis, and nail changes as assessed by the BASDAI, LEI, LDI-Basic and Physician Global Assessment of Nail Disease Activity (Nail VAS) at Day 169 and Day 365 (Open-label Day197)
- To determine the mean change from baseline in fatigue at Day 169 and Day 365 (Open-label Day 197) as assessed by the FACIT-Fatigue
- To determine the proportion of subjects with positive immunogenicity response up to Day 365 (Open-label Day 197)
- To assess safety by the proportion of subjects with adverse events (all AEs, deaths, SAEs, and AEs leading to discontinuation) and the proportion of subjects with laboratory marked abnormalities up to Day 729 (Open-label Day 561)
- To determine PK and exposure-response relationship of SC abatacept in PsA
- To identify potential systemic (serum cytokine, peripheral T-cell phenotyping, and/or RNA)
- PD biomarkers that may correlate with exposure/response relationships

To identify systemic or local biomarkers for clinical response, prognosis, subject stratification, or differentiation from internal or external compounds.

Outcomes/endpoints

The primary endpoint was proportion of ACR 20 responders at Day 169.

Key secondary endpoints at Day 169, in hierarchical order: Proportion of HAQ responders (a reduction of at least 0.35 from baseline), proportion of ACR 20 responders in the TNFi-naive subpopulation, proportion

of ACR 20 responders in the TNFi-exposed subpopulation, and proportion of x-ray non-progressors in total PsA-modified SHS (defined as a change from baseline in total PsA-modified SHS ≤0).

Other secondary endpoints at Day 169: Proportion of subjects achieving a PASI 50 in subjects with baseline BSA ≥ 3%; proportions of ACR 50 and ACR 70 responders.

Exploratory endpoints at Day 169: Proportion of subjects with Minimal Disease Activity (MDA), Disease Activity Score 28-C-reactive protein (DAS28-CRP) remission (defined as DAS28-CRP < 2.6), and DAS28-CRP low disease activity score (LDAS; defined as DAS28-CRP ≤ 3.2); proportion of subjects achieving a target lesion improvement of 50% (TL 50); mean change from baseline in DLQI (Dermatology Life Quality Index), Nail-VAS (scale for nail disease), BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), mCPDAI and PASDAS (modified Composite Psoriatic Disease Activity Index and Psoriatic Arthritis Disease Activity Score, composite measures of PsA), LEI (Leeds Enthesitis Index), and LDI-Basic (Leeds Dactylitis Index); and SF-36 (short-form-36 of mental and physical function including Mental Component Summary [MCS] and Physical Component Summary [PCS]).

Day 365 (Year 1/Open-label [OL] Day 197) efficacy assessments were exploratory objectives (Clinical Study Report Addendum 01 for Study IM101332).

Sample size

A total of 400 randomized subjects (200 per arm) were determined to yield > 99% power to detect a treatment effect in ACR 20 responder rate between the abatacept arm (41%) and the placebo arm (18%) at Day 169 at the 5% significance level. The sample size determination was done in such a way that the power was at least 80% for each of the endpoints included in the hierarchical testing procedure, and for the skin endpoint, PASI 50.

Randomisation

Randomization was stratified globally by current MTX use, prior use of TNFi therapy, and psoriasis involving ≥ 3% of the skin body surface area (BSA). Up to approximately 40% of subjects with < 3% BSA psoriatic skin involvement were planned to be randomized.

Blinding (masking)

Abatacept for injection was supplied as pre-filled, ready-to-use, glass syringes each containing 125-mg of abatacept per syringe (125 mg/mL). Placebo matching abatacept was also supplied as pre-filled, ready-to-use glass syringes.

Statistical methods

All efficacy analyses were performed using the intent-to-treat (ITT) analysis population, except if stated otherwise. Formal statistical testing (using the Cochran-Mantel Haenszel Chi-Squared test) was conducted for the primary and the key secondary efficacy endpoints. A hierarchical approach for statistical testing was performed for the key secondary endpoints. This procedure allowed for preserving of the overall Type I error rate of 0.05 for the study.

P-values were presented for each of these endpoints. However, endpoints were not significant if they had a rank lower than that endpoint whose null hypothesis was the first that could not be rejected at the 5%

significance level. Thus, any relevant measures that were below a measure that was not significant in the hierarchy were presented with nominal p-values.

The following imputation for all binary responder analyses of the double-blind ST Period was applied: 1) Early Escape subjects were imputed as non-responders at Days 141 and 169 for all binary responder analyses (for the radiographic analysis, Early Escape subjects were imputed as progressors at Day 169); 2) for subjects who discontinued the trial during the ST Period after receiving study medication, missing data was imputed as a non-responder at all scheduled protocol visits subsequent to the point of discontinuation up to Day 169 (for the radiographic analysis, a progressor imputation was applied). The above imputation method was used for the primary analyses of all binary response variables. For the most important binary response variables, additional analyses were provided with Days 141 and 169 for subjects designated Early Escape imputed using the observed data from Open-label Day 29 and Day 57.

For the longitudinal repeated measures analyses of the continuous variables during the double-blind ST Period, the measurements for the Early Escape subjects were set to missing at Days 141 and 169. For the key continuous variables, additional analyses were provided with Days 141 and 169 for subjects designated Early Escape imputed using the observed data from Open-label Day 29 and Day 57.

Results

Participant flow

ST Period

Among the 489 subjects enrolled in the study, 424 were randomly assigned to treatment. The primary reasons that enrolled subjects were not randomized (65/489, 13%) were failure to meet study criteria (45 subjects, 9%) and withdrawal of consent (15 subjects, 3%).

All 424 (abatacept n = 213; placebo n = 211) randomized subjects received at least 1 dose of double-blind study drug in the Treatment Period. Overall, 76/213 (35.7%) of subjects in the abatacept group and 89/211 (42.2%) of subjects in the placebo group were designated as Early Escape; these subjects left the double-blind treatment period and transitioned to the OL Period at Day 113. These subjects are listed under 'Discontinued due to Lack of Efficacy'. Overall, 52.6% of subjects completed the 6-month, double blind ST Period (see Table 28).

Additional 5 and 12 subjects in the abatacept and placebo groups, respectively, discontinued the study during the double-blind period due to lack of efficacy. Four subjects discontinued the study during the ST Period due to an AE (1 in the abatacept group and 3 in the placebo group). One additional subject in each group completed the ST Period but did not enter the Open-label Period due to reported lack of efficacy; 2 additional subjects in the abatacept group and 1 subject in the placebo group completed the ST Period but were not treated in the Open-label Period due to an AE.

Table 28 - Subject Disposition - Reasons for Discontinuation during the Short-term Period - ITT Population

	Number (%) of Subjects		
	Abatacept SC N=213	Placebo N=211	Total N=424
Number Discontinued	88 (41.3)	113 (53.6)	201 (47.4)
Death	0	0	0
Adverse event	1 (0.5)	3 (1.4)	4 (0.9)
Lack of efficacy [a]	81 (38.0)	101 (47.9)	182 (42.9)
Lack of joint efficacy	42 (19.7)	51 (24.2)	93 (21.9)
Lack of skin efficacy	3 (1.4)	2 (0.9)	5 (1.2)
Lack of skin and joint efficacy	36 (16.9)	48 (22.7)	84 (19.8)
Early escape [b]	76 (35.7)	89 (42.2)	165 (38.9)
Lost to follow-up	0	0	0
Subj request to discontinue study trt	2 (0.9)	3 (1.4)	5 (1.2)
Subject withdrew consent	3 (1.4)	5 (2.4)	8 (1.9)
Subject no longer meets study criteria	1 (0.5)	0	1 (0.2)
Poor/non-compliance	0	0	0
Pregnancy	0	0	0
Administrative reason by sponsor	0	0	0
Other	0	1 (0.5)	1 (0.2)
Number Completed Period	125 (58.7)	98 (46.4)	223 (52.6)

[a] In Study IM101332, Most of the subjects who discontinued for lack of efficacy were Early Escape subjects who were directed by the protocol to transition to the open-label period. Five (5) subjects in the abatacept group and 12 subjects in the placebo group (who completed the ST or who were early escape subjects) did not transition to the open-label period.
[b] Counted as discontinued due to Lack of Efficacy.
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Open-label period (Clinical Study Report Addendum 01 for Study IM101332)

Overall, 382 subjects entered the OL Period (abatacept, N = 197; placebo, N = 185; see Table 29). Overall, 14.4% of subjects discontinued the OL Period (16.2% of subjects in the abatacept group and 12.4% of subjects in the placebo group); most subjects discontinued the period due to lack of efficacy. In addition, 17 (4.5%) subjects who completed the OL Period were not treated in the LTE Period. Overall, 162 subjects (abatacept, N = 74; placebo, N = 88) who entered the OL Period were Early Escape subjects. Of these subjects, 24.3% and 14.8% of subjects, respectively, discontinued the period, most due to lack of efficacy.

At the time of the 1-year database lock, the LTE Population consisted of 310 subjects (abatacept, N = 153; placebo, N = 157); 12 (7.8%) and 14 (8.9%) subjects, respectively, discontinued this period.

Table 29 - Subject Disposition - Reasons for Discontinuation During the Open-label Period - Open-label Population

	Number (%) of Subjects		
	Abatacept SC N=197	Placebo N=185	Total N=382
Number Discontinued	32 (16.2)	23 (12.4)	55 (14.4)
Death	0	0	0
Adverse event	3 (1.5)	6 (3.2)	9 (2.4)
Lack of efficacy	19 (9.6)	10 (5.4)	29 (7.6)
Lack of joint efficacy	5 (2.5)	2 (1.1)	7 (1.8)
Lack of skin efficacy	4 (2.0)	2 (1.1)	6 (1.6)
Lack of joint and skin efficacy	10 (5.1)	6 (3.2)	16 (4.2)
Lost to follow-up	1 (0.5)	2 (1.1)	3 (0.8)
Subj request to discontinue study trt	4 (2.0)	3 (1.6)	7 (1.8)
Subject withdrew consent	4 (2.0)	2 (1.1)	6 (1.6)
Subject no longer meets study criteria	0	0	0
Poor/non-compliance	1 (0.5)	0	1 (0.3)
Pregnancy	0	0	0
Administrative reason by sponsor	0	0	0
Other	0	0	0
Number Ongoing	0	0	0
Number Completed Period	165 (83.8)	162 (87.6)	327 (85.6)

Recruitment

A total of 76 sites worldwide enrolled subjects in this study (US - 15, Canada - 2, Mexico - 7, Brazil - 2, Columbia - 3, Chile - 3, Argentina - 6, Peru - 3, Israel - 5, Germany - 7, Poland - 2, Czech Republic - 3, France - 5, Spain - 3, South Africa - 5, Greece - 3, and Italy – 2).

Study Initiation Date: 19-Jun-2013

Study Completion Date: 05-Oct-2015 (interim database lock)

Clinical Study Report Addendum 01: Study Completion Date: 22-Apr-2016 (database lock).

Conduct of the study

Protocol deviations

There were 177 significant protocol deviations in 132 subjects as of the date of database lock; 34 of the significant deviations were also relevant deviations.

Relevant deviations were considered to have the potential to affect the primary analysis and therefore, were considered relevant only for the ST Period (first 6 months of treatment). 39 subjects had relevant protocol deviations, including 19 (9%) subjects in the abatacept group and 20 (9%) subjects in the placebo group. The most common relevant protocol deviation in the abatacept group was need for washout due to subjects receiving TNFi therapy within 8 weeks of randomization (4.2%), and in the placebo group was subjects meeting criteria for Early Escape, but were not assessed as such by the investigator, resulting in the subject not entering the Open-label Period at Day 113 (2.8%).

Changes in the Conduct of the Study

There were 9 amendments to the protocol. There were no changes to the planned analysis. Post hoc analyses were performed to further describe specific treatment effects.

Baseline data

The 2 treatment groups were balanced with respect to demographic characteristics at entry into the ST Period (see Table 30; includes also data for Study IM010332). The overall mean age was 50.4 years (range: 22 to 81 years), 55% of subjects were female, and most subjects were White (92.7%). A total of 20% of subjects were from sites in North America, 26% from Europe, and 41% from South America, 13% from the Rest of the World (ROW).

Table 30 - Baseline Disease Characteristics, Study IM101332 (ITT Population) and Study IM101158 (All Randomized and Treated Subjects)

	Study IM101332			Study IM101158				
	ABA SC 125 mg N=213	Placebo N=211	Total N=424	ABA IV 30/10 mg/kg N=43	ABA IV 10/10 mg/kg N=40	ABA IV 3/3 mg/kg N=45	Placebo N=42	Total N=170
BSA Affected (CRF)								
≥ 3% (n [%])	146 (68.5)	148 (70.1)	294 (69.3)	20 (46.5)	21 (52.5)	21 (46.7)	21 (50.0)	83 (48.8)
< 3% (n [%])	67 (31.5)	63 (29.9)	130 (30.7)	23 (53.5)	19 (47.5)	24 (53.3)	21 (50.0)	87 (51.2)
Duration of PsA (years)								
Mean (SD)	8.3 (8.1)	8.8 (8.3)	8.5 (8.2)	7.8 (7.7)	10.6 (9.4)	7.2 (7.4)	7.4 (8.0)	8.2 (8.2)
Median	6.0	6.0	6.0	5.0	9.5	5.0	4.0	6.0
Min-Max	0-45	0-44	0-45	0-31	0-39	0-38	0-28	0-39
Tender Joints								
Mean (SD)	21.0 (13.4)	19.3 (13.1)	20.2 (13.3)	19.6 (11.4)	25.2 (15.6)	22.7 (14.6)	21.3 (15.3)	22.2 (14.3)
Median	18.0	16.0	17.0	19.0	22.5	19.0	16.0	19.0
Min-Max	3-68	3-68	3-68	4-54	7-64	4-68	3-59	3-68
Swollen Joints								
Mean (SD)	12.1 (7.8)	11.1 (7.2)	11.6 (7.5)	10.3 (7.1)	12.5 (8.7)	10.3 (6.9)	10.5 (7.9)	10.9 (7.6)
Median	10.0	9.0	9.0	9.0	10.0	7.0	7.0	9.0
Min-Max	3-41	3-36	3-41	3-43	3-41	3-36	3-37	3-43
Subject Assessment of Pain								
Mean (SD)	64.2 (23.5)	64.4 (21.8)	64.3 (22.6)	58.0 (20.8)	67.5 (20.6)	58.2 (27.4)	62.1 (25.8)	61.3 (24.0)
Median	67.0	69.0	68.0	62.0	68.0	61.5	65.5	65.0
Min-Max	3-100	0-100	0-100	11-96	17-100	0-97	9-99	0-100
HAQ-Disability Index								
Mean (SD)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)	1.2 (0.8)	1.3 (0.7)	1.1 (0.7)	1.2 (0.7)	1.2 (0.7)
Median	1.4	1.3	1.4	1.0	1.4	1.1	1.3	1.3
Min-Max	0.0-3.0	0.0-2.9	0.0-3.0	0.0-2.6	0.0-2.6	0.0-2.4	0.0-2.4	0.0-2.6
Subject Global Assessment								
Mean (SD)	61.1 (23.5)	62.6 (22.6)	61.9 (23.1)	55.6 (21.5)	60.8 (22.9)	59.5 (22.1)	58.6 (26.5)	58.6 (23.2)
Median	62.0	65.0	63.0	59.0	66.5	63.5	65.5	62.0
Min-Max	2-100	3-100	2-100	17-96	16-99	6-98	9-97	6-99
Physician Global Assessment								
Mean (SD)	53.9 (18.8)	55.0 (19.6)	54.4 (19.2)	56.7 (19.4)	57.3 (19.8)	54.7 (17.7)	52.6 (18.6)	55.3 (18.8)
Median	55.0	57.0	55.0	59.0	58.5	57.0	53.5	57.0
Min-Max	8.0-95.0	8.0-100.0	8-100	16-98	4-86	13-89	5-94	4-98
CRP (mg/dL)								
Mean (SD)	1.4 (2.1)	1.4 (3.0)	1.4 (2.6)	2.2 (5.2)	1.5 (1.8)	1.8 (2.4)	1.3 (2.7)	1.7 (3.3)
Median	0.6	0.6	0.6	0.7	1.1	0.7	0.7	0.9
Min-Max	0.0-18.2	0.0-26.6	0.0-26.6	0.0-33.9	0.0-8.9	0.0-9.4	0.0-17.1	0.0-33.9
PASI (BSA ≥ 3 at BL)								
Mean (SD)	7.4 (8.0)	7.2 (7.8)	7.3 (7.8)	16.3 (17.8)	9.4 (9.2)	11.7 (8.4)	13.1 (10.5)	12.6 (12.0)
Median	4.5	4.5	4.5	8.9	5.6	9.4	9.0	8.6
Min-Max	0.0-47.0	0.0-44.0	0.0-47.0	1.6-72.0	1.2-38.9	1.0-30.0	2.7-39.1	1.0-72.0
Target Lesion Score								
Mean (SD)	5.4 (2.3)	5.4 (2.2)	5.4 (2.2)	6.6 (2.8)	6.0 (2.4)	5.5 (2.7)	6.4 (2.7)	6.1 (2.7)
Median	5.0	5.0	5.0	6.0	2.4	5.0	6.5	6.0
Min-Max	2-12	1-12	1-12	2-12	2-12	1-12	1-12	1-12
Previously Exposed to TNFi, n (%)								
	129 (60.6)	130 (61.6)	259 (61.1)	22 (51.2)	13 (32.5)	16 (35.6)	12 (28.6)	63 (37.1)

Abbreviations: ABA - abatacept, BL - baseline, BSA - body surface area, CRF - case report form, CRP - C-reactive protein, CSR - clinical study report, HAQ - health assessment questionnaire, ITT - intent-to-treat, IV - intravenous, PASI - Psoriasis Area and Severity Index, PsA - psoriatic arthritis, SC - subcutaneous, SD - standard deviation, TNFi - tumor necrosis factor-α inhibitor

In subjects who had prior TNFi exposure, 60% (80/129) and 62% (81/130) of TNFi-exposed subjects in the abatacept and placebo groups, respectively, were documented as having failed at least one TNFi due to inadequate efficacy. Additionally, 16.5% (35/129) and 18.0% (38/130) of TNFi-exposed subjects in the abatacept and placebo groups, respectively, were exposed to more than 1 prior TNFi therapy.

Table 31 - Summary of Reason of Prior TNFi Failure - ITT Population

	Number (%) of Subjects	
	Abatacept SC (N=213)[a]	Placebo (N=211)[a]
INADEQUATE EFFICACY RESPONSE	80 (37.6)	81 (38.4)
INTOLERABILITY	18 (8.5)	13 (6.2)
OTHER	40 (18.8)	44 (20.9)

[a] Total subjects in the study.
A subject can be counted in 2 categories.
The category 'Other' includes reasons unknown for prior TNFi failure.

Concomitant Therapy

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 ST Period up to the last dose (see Table 32). The mean daily dose of MTX was similar to baseline during the ST Period for both treatment groups. 2 subjects in the abatacept group were reported as having taken concomitant etanercept and 1 subject in the placebo group received concomitant tocilizumab. The Sponsor confirmed with the investigational centres that the 3 subjects terminated biologic treatment prior to first dose of study drug in accordance with protocol-specified washout periods, but no stop dates had been recorded in the CRFs.

Overall, few patients received rescue medication during the ST Period. The number of patients receiving systemic steroids (oral), localized steroids (IM, IA, entheseal), or topical steroids was higher in the placebo group compared to the abatacept group.

Table 32 - Anti-rheumatic Medications Summary at Baseline and During the Short-term Period up to the Last Dose - ITT Population

	At Day 1 (Baseline)		During the ST Period	
	Abatacept SC (N=213) n (%)	Placebo (N=211) n (%)	Abatacept SC (N=213) n (%)	Placebo (N=211) n (%)
Total Subjects on CONMEDS	204 (95.8)	203 (96.2)	209 (98.1)	208 (98.6)
NSAIDS	137 (64.3)	142 (67.3)	142 (66.7)	150 (71.1)
DMARDS	147 (69.0)	145 (68.7)	147 (69.0)	146 (69.2)
METHOTREXATE	129 (60.6)	127 (60.2)	129 (60.6)	128 (60.7)
LEFLUNOMIDE	15 (7.0)	13 (6.2)	15 (7.0)	13 (6.2)
SULFASALAZINE	12 (5.6)	11 (5.2)	12 (5.6)	11 (5.2)
HYDROXYCHLOROQUINE	0	1 (0.5)	0	1 (0.5)
MTX Dose (SD)	17.1 (7.0)	17.1 (9.2)	16.9 (7.0)[a]	16.9 (9.3)[a]
Biologics	2 (0.9)	1 (0.5)	2 (0.9)	1 (0.5)
TOCILIZUMAB	0	1 (0.5)	0	1 (0.5)
TNFi Therapy	2 (0.9)	0	2 (0.9)	0
ETANERCEPT	2 (0.9)	0	2 (0.9)	0
Corticosteroids				
Topical Low Potency	4 (1.9)	7 (3.3)	6 (2.8)	13 (6.2)
Topical High/Medium Potency	7 (3.3)	8 (3.8)	8 (3.8)	11 (5.2)
Oral and/or injectable	56 (26.3)	51 (24.2)	69 (32.4)	68 (32.2)
Oral	56 (26.3)	51 (24.2)	62 (29.1)	59 (28.0)
Mean Oral Dose mg (SD)	6.8 (2.7)	6.3 (2.6)	8.0 (5.4)	8.0 (4.9)

[a] Dose at Day 169 (Table S.4.12)
The mean oral dose of corticosteroids (prednisone equivalents) includes only subjects who had taken at least 1 dose of oral corticosteroids.

Numbers analysed

Efficacy and safety data from all subjects were analysed according to the treatment group assignment in accordance with the randomization schedule (see Table 33 and Table 34).

Table 33 - Analysis Populations

Population	Number of Subjects		
	Abatacept	Placebo	Total
ITT/As Treated (ST Period)	213	211	424
Open-label	197	185	382
Cumulative Abatacept Population	213	185	398
Open-label, Early Escape	73	87	160
Long-term, Early Escape	43	60	103
Immunogenicity Analysis Population	206	203	409
PK Analysis Population	213	NA	213

Source: Table 5.1.1-1; Section 9.1, Section 10, and Section 11

Table 34 - Analysis Populations (*Clinical Study Report Addendum 01 for Study IM101332)*

Population	Number of Subjects		
	Abatacept	Placebo	Total
ITT/As Treated (Month 6)	213	211	424
Open-label (Year 1)	197	185	382
Open-label, Early Escape	74	88	162
Long-term Extension Population (Year 2)	153	157	310
Long-term, Early Escape (Year 2)	56	73	129
Cumulative Abatacept Population[a]	213	185	398
Immunogenicity Analysis Population	209	184	393
PK Analysis Population	162	153	315

[a] Cumulative abatacept population is for safety analyses only.
Source: Table 5.1-1; Section 9, Section 10, and Section 11

Outcomes and estimation

Primary Efficacy Endpoint

The primary endpoint for the ITT analysis population was the proportion of ACR 20 responders at Day 169, which was statistically superior for the abatacept group compared to the placebo group (see Table 35). A significantly higher proportion of subjects in the abatacept group, compared to the placebo group, met the criteria for ACR 20 response at Day 169.

Table 35 - Proportion of Subjects with ACR 20 Response at Day 169 – ITT Population

Study Day			Abatacept SC (N=213)	Placebo (N=211)
Day 169	ACR 20	Number of subjects n/m (%)	84/213 (39.4%)	47/211 (22.3%)
		95% CI	(32.9, 46.0)	(16.7, 27.9)
		Relative Risk (95% CI)	1.77 (1.31, 2.39)	N/A
		Estimate of Difference (95% CI)	17.2 (8.7, 25.6)	N/A
		p-value	<0.001	N/A

n = Number of subjects with ACR 20 response, m = Number of subjects in the analysis.
P-value is based on the CMH Chi-square test stratified by MTX use, prior TNFi and BSA.
Estimate and 95% CI for difference is based on stratum size weights method with stratification by MTX use, prior TNFi and BSA.
N/A = Not applicable
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 period were imputed as non-responders.

ACR 20 Response Over Time in the Short-term Period: Figure 23 presents ACR 20 response rate over time for the ITT Population, and shows the primary analysis in which the Early Escape subjects are imputed as non-responders at Days 141 and 169 for ACR 20. Figure 24 shows the primary analysis with the superimposed additional analysis in which ACR 20 responses for Early Escape subjects at Day 141 and Day 169 are calculated based on the observed values at Open-label Days 29 and 57. The analysis showed a numeric improvement in the placebo group after early Early Escape subjects had transitioned to abatacept, and continued improvement in the abatacept group at Days 141 and 169.

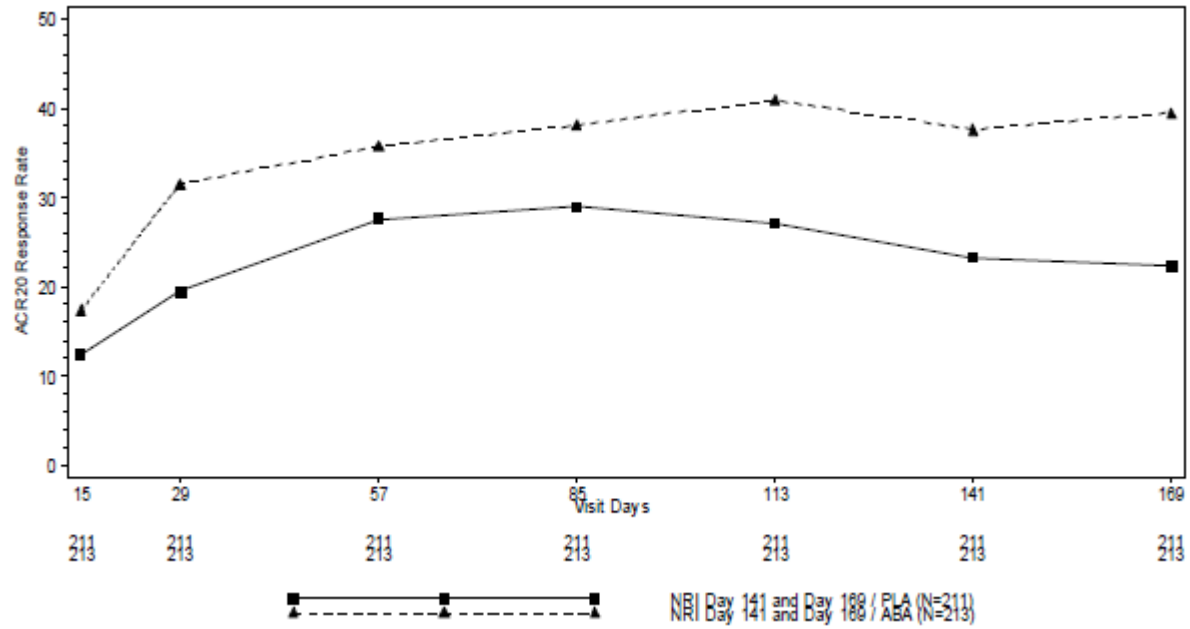

Figure 23 - ACR 20 Response Over Time During Short-term Period - Non-responder Imputation for Early Escape Subjects at Day 141 and 169 - ITT Population

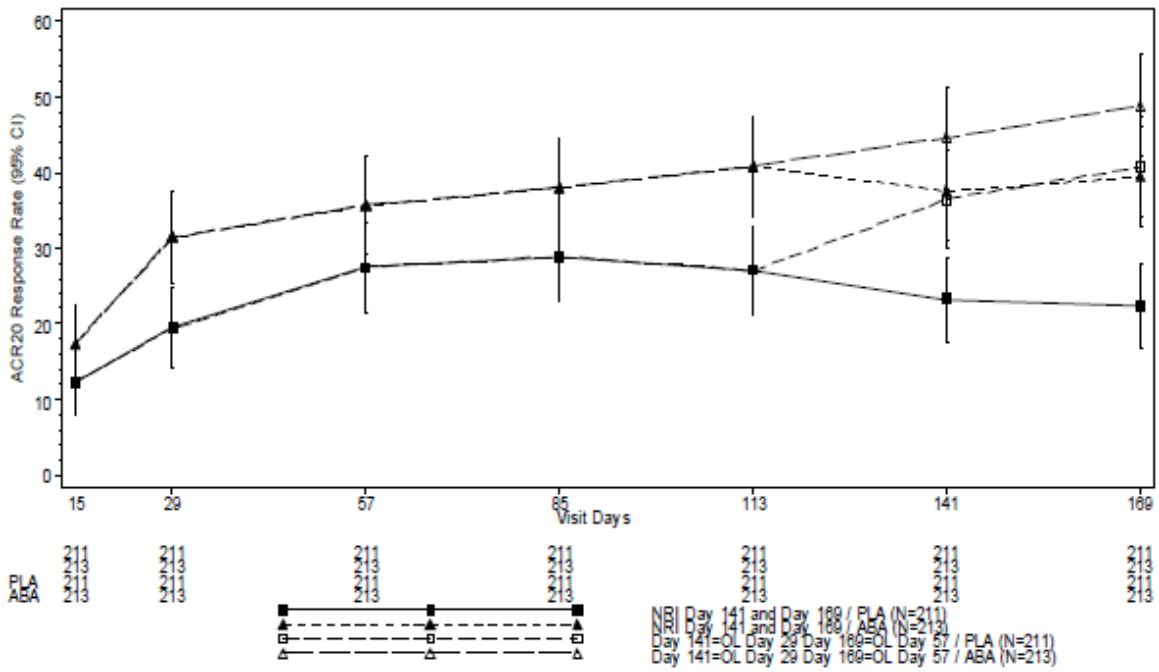

Figure 24 - ACR 20 Response Over Time During Short-term Period

ACR 20 Responses at Day 169 by Subgroups: In both treatment groups, the proportion of subjects with an ACR 20 response was numerically higher in subgroups that used MTX, non-biological DMARDs, and corticosteroids at baseline compared to subjects who did not report use of these agents at baseline (see Table 36).

Table 36 - Proportion of Subjects with ACR 20 Response at Day 169 by Subgroups – ITT Population

Subgroup		Abatacept SC (N=213)	Placebo (N=211)
MTX Use at Day 1: Yes	Number of subjects n/m (%)	57/129 (44.2%)	37/127 (29.1%)
	95% CI	(35.6, 52.8)	(21.2, 37.0)
	Estimate of Difference (95% CI)	15.05 (3.40, 26.71)	N/A
MTX Use at Day 1: No	Number of subjects n/m (%)	27/84 (32.1%)	10/84 (11.9%)
	95% CI	(22.2, 42.1)	(5.0, 18.8)
	Estimate of Difference (95% CI)	20.24 (8.08, 32.39)	N/A
Non Biologic DMARD Use at Day 1: Yes	Number of subjects n/m (%)	66/147 (44.9%)	39/145 (26.9%)
	95% CI	(36.9, 52.9)	(19.7, 34.1)
	Estimate of Difference (95% CI)	18.00 (7.20, 28.81)	N/A
Non Biologic DMARD Use at Day 1: No	Number of subjects n/m (%)	18/66 (27.3%)	8/66 (12.1%)
	95% CI	(16.5, 38.0)	(4.2, 20.0)
	Estimate of Difference (95% CI)	15.15 (1.83, 28.47)	N/A
Oral Steroid Use at Day 1: Yes	Number of subjects n/m (%)	26/56 (46.4%)	11/51 (21.6%)
	95% CI	(33.4, 59.5)	(10.3, 32.9)
	Estimate of Difference (95% CI)	24.86 (7.60, 42.12)	N/A
Oral Steroid Use at Day 1: No	Number of subjects n/m (%)	58/157 (36.9%)	36/160 (22.5%)
	95% CI	(29.4, 44.5)	(16.0, 29.0)
	Estimate of Difference (95% CI)	14.44 (4.50, 24.39)	N/A

n = Number of subjects with ACR 20 response, m = Number of subjects in the analysis. 95% CI for difference is based on normal approximation.
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 period were imputed as non-responders.

Key Secondary Efficacy Endpoints

Key secondary endpoints are presented in Table 37 in hierarchical order (Day 169). Because the treatment difference for HAQ response rate was not significant at the 5% significance level, treatment differences for endpoints lower in the testing hierarchy (ie, ACR 20 response rate at Day 169 in the TNFi-naive and TNFi-exposed cohorts and x-ray non-progressor rate at Day 169) could not be tested for significance. Thus, for these endpoints, nominal p-values are provided.

Table 37 - Summary of Key Secondary Endpoints

Endpoint (Day 169)	Abatacept N - 213	Placebo N = 211
HAQ response[a]		
Subjects, n/N (%)	66/213 (31.0)	50/211 (23.7)
95% CI	24.8, 37.2	18.0, 29.4
Estimate of Difference (95% CI); p-value	7.2 (-1.1, 15.6); 0.097	
ACR 20 response, TNFi-naive		
Subjects, n/N (%)	37/84 (44.0)	18/81 (22.2)
95% CI	(33.4, 54.7)	(13.2, 31.3)
Estimate of Difference (95% CI); p-value	21.9 (8.3, 35.6); 0.003[b]	
ACR 20 response, TNFi-exposed		
Subjects, n/N (%)	47/129 (36.4)	29/130 (22.3)
95% CI	(28.1, 44.7)	(15.2, 29.5)
Estimate of Difference (95% CI); p-value	~~21.9 (8.3, 35.6)~~ 14.0 (3.3, 24.8); 0.012[b]	
Radiographic non-progression[c]		
Subjects, n/N (%)	91/213 (42.7)	69/211 (32.7)
95% CI	36.1, 49.4	26.4, 39.0
Estimate of Difference (95% CI); p-value[b]	10.0 (1.0, 19.1); 0.034[b]	

Abbreviations: ACR = American College of Rheumatology; TNFi - tumor necrosis factor-α inhibitor.
[a] Mean decrease from baseline ≥ 0.35.
[b] Because the treatment difference for HAQ response rate was not significant at the 5% significance level, treatment differences for endpoints lower in the testing hierarchy could not be tested at the 5% significance level preserving the type I error; nominal p values are presented.
[c] Radiographic non-progression: change from baseline in Total SHS ≤ 0.
[d] Due to the high rate of progressor imputation and the slow radiographic progression, the interpretation of the radiographic non progression rate is difficult.
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 ACR 20 and HAQ response analyses and as non-progressors for radiographic analyses at Day 169.

Although the proportion of subjects with HAQ response (decrease of at least 0.35 from baseline) at Day 169 was numerically higher in the abatacept group than the placebo group, the difference between the abatacept and placebo groups was not significant (see above Table 37). Figure 25 shows a) the analysis for which the Early Escape subjects are imputed as non-responders at Days 141 and 169 and b) the additional analysis for which HAQ scores for Early Escape subjects at Day 141 and Day 169 are calculated based on the observed values at Open-label Days 29 and 57. The analysis showed numeric improvement in the placebo group after Early Escape subjects had transitioned to abatacept, and continued improvement in the abatacept group.

The adjusted mean change from baseline in the HAQ-DI was numerically greater in the abatacept group vs the placebo group in both the TNFi-naive and the TNFi-exposed populations at Day 169 and at the majority of assessment time points.

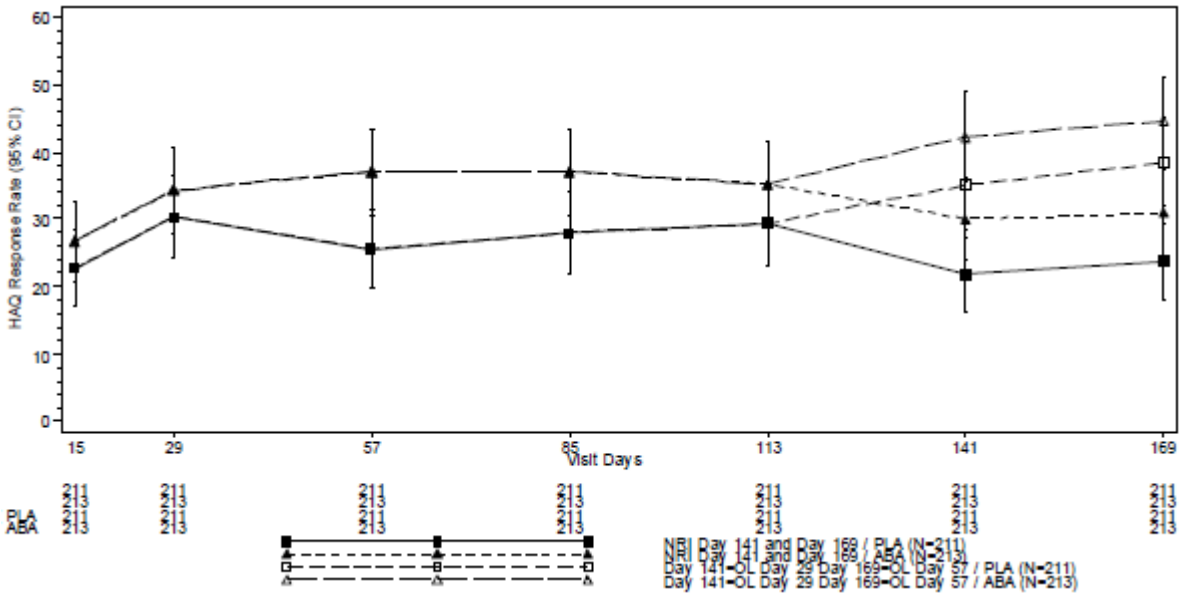

Figure 25 - HAQ Response Over Time During Short-term Period - ITT Population

ACR 20 Responders in the TNFi-naive and TNFi-exposed Subpopulations: A higher proportion of subjects in the abatacept group, compared to the placebo group, met the ACR 20 criteria for responders at Day 169 in both the TNFi-naive and TNFi-exposed subpopulations (see above Table 37).

Non-progression in Total SHS: The proportion of radiographic non-progressors in total PsA-Modified Sharp van der Heijde score (SHS) at Day 169 in the ITT Population was greater in the abatacept group than in the placebo group, with a nominal p-value of 0.034 (see above Table 37). The proportion of radiographic non-progressors in erosion and JSN scores at Day 169 in the ITT Population was numerically greater in the abatacept group than in the placebo group (see Table 38). The adjusted mean change from baseline in the total SHS was slightly higher in the abatacept group vs the placebo group at Day 169 (0.48 vs. 0.36).

Table 38 - Proportion of Radiographic Non-Progressors in Erosion and Joint Space Narrowing Score at Day 169 - ITT Population

		Abatacept SC (N=213)	Placebo (N=211)
Change from baseline <=0			
Erosion Score	Number of subjects (%)	98/213 (46.0%)	73/211 (34.6%)
	95% CI	(39.3, 52.7)	(28.2, 41.0)
Joint Space Narrowing Score	Number of subjects (%)	90/213 (42.3%)	78/211 (37.0%)
	95% CI	(35.6, 48.9)	(30.5, 43.5)

PsA-modified Sharp/Van der Heijde Scoring.
n = Number of Non-progressors, m = Number of subjects in the analysis.

Other Secondary endpoints

A greater proportion of subjects in the abatacept group vs the placebo group achieved at least 50% improvement in PASI (PASI 50) scores at Day 169 (see Table 39). The proportion of subjects who achieved at least 50% improvement in the PASI was greater in the abatacept vs the placebo group at each time point. As with the ACR 20 and HAQ results, when the observed data from Open-label days 29 and 57 was used for Study Days 141 and 169 for the Early Escape subjects, improvement in the PASI 50

was seen in the placebo group after switching to abatacept, and continued benefit was also seen in the abatacept group.

Table 39 - Proportion of Subjects (with BSA>=3%) Achieving PASI 50 at Day 169 - ITT Population

Study Day		Abatacept SC (N=146)	Placebo (N=148)
Day 169	PASI 50		
	Number of subjects n/m (%)	39/146 (26.7%)	29/148 (19.6%)
	95% CI	(19.5, 33.9)	(13.2, 26.0)
	Relative Risk (95% CI)	1.37 (0.90, 2.09)	N/A
	Estimate of Difference (95% CI)	7.3 (-2.2, 16.7)	N/A
	p-value	0.137	N/A

n = Number of subjects achieving PASI 50; m = Number of subjects in the analysis.
Estimate and 95% CI for difference is based on stratum size weights method with stratification by MTX use and prior TNF.
P-value is based on the CMH Chi-square test stratified by MTX use and prior TNF.
N/A = Not applicable

A numerically higher proportion of subjects in the abatacept group, compared to the placebo group, met the criteria for an ACR 50 response at Day 169 (19.2% vs. 12.3% when Early Escape/missing subject data was imputed as non-responders). The corresponding rates for ACR 70 response at Day 169 were 10.3% vs. 6.6%, respectively (see Table 40 and Table 41).

Table 40 - Proportion of Subjects with ACR 50/ACR 70 Response at Day 169 - ITT Population

		Abatacept SC (N=213)	Placebo (N=211)
ACR 50*	Number of subjects n/m (%)	41/213 (19.2%)	26/211 (12.3%)
	95% CI	(14.0, 24.5)	(7.9, 16.8)
	Estimate of Difference (95% CI)	6.9 (0.1, 13.7)	N/A
ACR 70*	Number of subjects n/m (%)	22/213 (10.3%)	14/211 (6.6%)
	95% CI	(6.2, 14.4)	(3.3, 10.0)
	Estimate of Difference (95% CI)	3.7 (-1.5, 8.9)	N/A

n = Number of subjects with ACR 50/ACR 70 response, m = Number of subjects in the analysis.
*Early Escape: Imputation as Non-responders at Day 141 and Day 169
Estimate and 95% CI for difference is based on stratum size weights method with stratification by MTX use, prior TNFi and BSA.
N/A = Not applicable

Table 41 - Proportion of Subjects with ACR 50/ACR 70 Response at Day 169 by Prior TNFi Use - ITT Population

Subgroup / Study Day			Abatacept SC (N=213)	Placebo (N=211)
No Prior TNF				
Day 169	ACR 50	Number of subjects n/m (%)	21/84 (25.0%)	12/81 (14.8%)
		95% CI	(15.7, 34.3)	(7.1, 22.6)
		Estimate of Difference (95% CI)	10.2 (-1.5, 22.0)	N/A
	ACR 70	Number of subjects n/m (%)	10/84 (11.9%)	7/81 (8.6%)
		95% CI	(5.0, 18.8)	(2.5, 14.8)
		Estimate of Difference (95% CI)	3.3 (-5.8, 12.4)	N/A
Prior TNFi				
Day 169	ACR 50	Number of subjects n/m (%)	20/129 (15.5%)	14/130 (10.8%)
		95% CI	(9.3, 21.7)	(5.4, 16.1)
		Estimate of Difference (95% CI)	4.7 (-3.4, 12.8)	N/A
	ACR 70	Number of subjects n/m (%)	12/129 (9.3%)	7/130 (5.4%)
		95% CI	(4.3, 14.3)	(1.5, 9.3)
		Estimate of Difference (95% CI)	3.9 (-2.4, 10.2)	N/A

n = Number of subjects with ACR 50/ACR 70 response, m = Number of subjects in the analysis.
Estimate and 95% CI for difference is based on stratum size weights method with stratification by MTX use and BSA.
N/A = Not applicable
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 period were imputed as non-responders.

Short Form-36/Health-Related Quality of Life: Subjects in the abatacept group achieved a numerically greater change from baseline in the physical function subscale than subjects in the placebo group. Changes in the mental function subscale were similar in both groups (see Table 42).

Table 42 - Adjusted Mean Change from Baseline at Day 169 in SF-36 (v2.0) Subscales and Summary Components (PCS and MCS) – ITT Population

Study Day			Abatacept SC N=213	Placebo N=211
Day 169	PCS	n	124	97
		Baseline Mean (SD)	33.95 (8.592)	34.03 (8.780)
		Post-Baseline Mean (SD)	40.58 (9.100)	39.81 (9.147)
		Adjusted Change from Baseline (SE)	5.11 (0.637)	3.69 (0.707)
		95% CI	(3.86, 6.36)	(2.30, 5.08)
		Adjusted Mean Difference from Placebo (95% CI)	1.42 (-0.32, 3.15)	
Day 169	MCS	n	124	97
		Baseline Mean (SD)	38.81 (12.669)	40.32 (12.361)
		Post-Baseline Mean (SD)	42.52 (11.320)	43.13 (11.252)
		Adjusted Change from Baseline (SE)	2.56 (0.826)	2.62 (0.924)
		95% CI	(0.93, 4.18)	(0.80, 4.44)
		Adjusted Mean Difference from Placebo (95% CI)	-0.06 (-2.32, 2.20)	

n = number of subjects with both post-baseline and baseline measurements; MCS =Mental Component Summary.
For Early Escape Subjects measurements are set to missing at Day 169.
The longitudinal model includes the fixed categorical effects of treatment, day, prior TNFi 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.
PCS=Physical Component Summary

Summary of the key endpoints for the OL Period (Year 1) (Clinical Study Report Addendum 01 for Study IM101332)

Day 365 (Year 1/Open-label [OL] Day 197) efficacy assessments were exploratory objectives. A summary of the key endpoints for the OL Period (Year 1) is presented in Table 43. ACR 20 Response over time during Short-term and Open-label Period is presented in Figure 26.

Table 43 - Summary of Key Endpoints up to Year 1

Endpoint	All ITT Subjects		TNFi-Naive Subjects		TNFi-Exposed Subjects	
	Aba/Aba N - 213	Placebo/Aba N = 211	Aba/Aba N - 84	Placebo/Aba N = 81	Aba/Aba N - 129	Placebo/Aba N = 130
ACR 20 response[a]						
Subjects, n/N (%)	103/213 (48.4)	104/211 (49.3)	46/84 (54.8)	46/81 (56.8)	57/129 (44.2)	58/130 (44.6)
95% CI	41.6, 55.1	42.5, 56.0	44.1, 65.4	46.0, 67.6	35.6, 52.8	36.1, 53.2
ACR 50 response[a]						
Subjects, n/N (%)	60/213 (28.2)	68/211 (32.2)	30/84 (35.7)	31/81 (38.3)	30/129 (23.3)	37/130 (28.5)
95% CI	22.1, 34.2	25.9, 38.5	25.5, 46.0	27.7, 48.9	16.0, 30.5	20.7, 36.2
ACR 70 response						
Subjects, n/N (%)	33/213 (15.5)	37/211 (17.5)	12/84 (14.3)	19/81 (23.5)	21/129 (16.3)	18/130 (13.8)
95% CI	10.6, 20.4	12.4, 22.7	6.8, 21.8	14.2, 32.7	9.9, 22.6	7.9, 19.8
DAS28-CRP[b]						
Adjusted mean change from baseline (SE)	-1.81 (0.093)	-1.84 (0.096)	-1.78 (0.133)	-1.92 (0.139)	-1.76 (0.130)	-1.72 (0.131)
HAQ response[c]						
Subjects, n/N (%)	85/213 (39.9)	82.211 (38.9)	39/84 (46.4)	35/81 (43.2)	46/129 (35.7)	47/130 (36.2)
95% CI	33.3, 46.5	32.3, 45.4	35.8, 57.1	32.4, 54.0	27.4, 43.9	27.9, 44.4
HAQ-DI[a,b]						
Adjusted mean change from baseline (SE)	-0.37 (0.041)	-0.38 (0.043)	-0.36 (0.062)	-0.43 (0.064)	-0.35 (0.056)	-0.33 (0.057)
Subjects with complete resolution of enthesitis[d]						
Subjects, n/N (%)	68/140 (48.6)	58/132 (43.9)	NA	NA	NA	NA
95% CI	40.3, 56.9	35.5, 52.4				
Subjects with complete resolution of dactylitis[d]						
Subjects, n/N (%)	42/61 (68.9)	30/50 (60.0)	NA	NA	NA	NA
95% CI	57.2, 80.5	46.4, 73.6				
BASDAI[b,e]						
Adjusted mean change from baseline (SE)	-2.40 (0.200)	-2.14 (0.201)	NA	NA	NA	NA
PASI 50 response[a,f]						
Subjects, n/N (%)	44/146 (30.1)	51/148 (34.5)	20/55 (36.4)	20/51 (39.2)	24/91 (26.4)	31/97 (32.0)
95% CI	22.7, 37.6	26.8, 42.1	23.7, 49.1	25.8, 52.6	17.3, 35.4	22.7, 41.2
PASI 75 response[a,f]						
Subjects, n/N (%)	29/146 (19.9)	25/148 (16.9)	15/55 (27.3)	9/51 (17.6)	14/91 (15.4)	16/97 (16.5)
95% CI	13.4, 26.3	10.9, 22.9	15.5, 39.0	7.2, 28.1	8.0, 22.8	9.1, 23.9
SF-36						
PCS, mean change from baseline (SE)	6.25 (0.648)	5.91 (0.664)	NA	NA	NA	NA
MCS, mean change from baseline (SE)	3.89 (0.719)	2.73 (0.737)	NA	NA	NA	NA
Radiographic non-progression in total SHS[g]						
Subjects, n/N (%)	112/213 (52.6)	115/211 (54.5)				
95% CI	45.9, 59.3	47.8, 61.2	NA	NA	NA	NA
Total SHS[b,g]						
Adjusted mean change from baseline (SE)	0.18 (0.121)	0.30 (0.124)	0.07 (0.170)	0.22 (0.178)	0.28 (0.172)	0.38 (0.173)

Abbreviation: Aba = abatacept.

[a] For Early Escape subjects measurements Day 141, 169, 197, 253 and 309 are measurements at Day 29 OL, Day 57 OL, Day 85 OL, Day 141 OL, Day 197 OL.

[b] The longitudinal model used for analysis; an unstructured covariance matrix is used to represent the correlation of the repeated measures within each subject.

[c] HAQ response is defined as an improvement of at least 0.35 units from baseline in the HAQ Disability Index.

[d] Enthesitis and dactylitis when present at baseline. For early escape subjects Day 169 is 197 days since start of study medication (Day 85 OL), and Day 365 is 309 days since start of study medication (Day 197 OL).

[e] For BASDAI: baseline value >=4. For Early Escape subjects: Day 169 is 197 days since start of study medication (Day 85 OL), and Day 365 is 309 days since start of study medication (Day 197 OL).

[f] Subjects with ≥3% BSA.

[g] For early escape subjects, the Day 365 x-ray is performed at Day 309 (Day 197 OL). For Early Escape Subjects the observed measurements at Day 169 (Day 57 of open-label) and Day 309 (Day 197 of open-label) are used in the analysis.

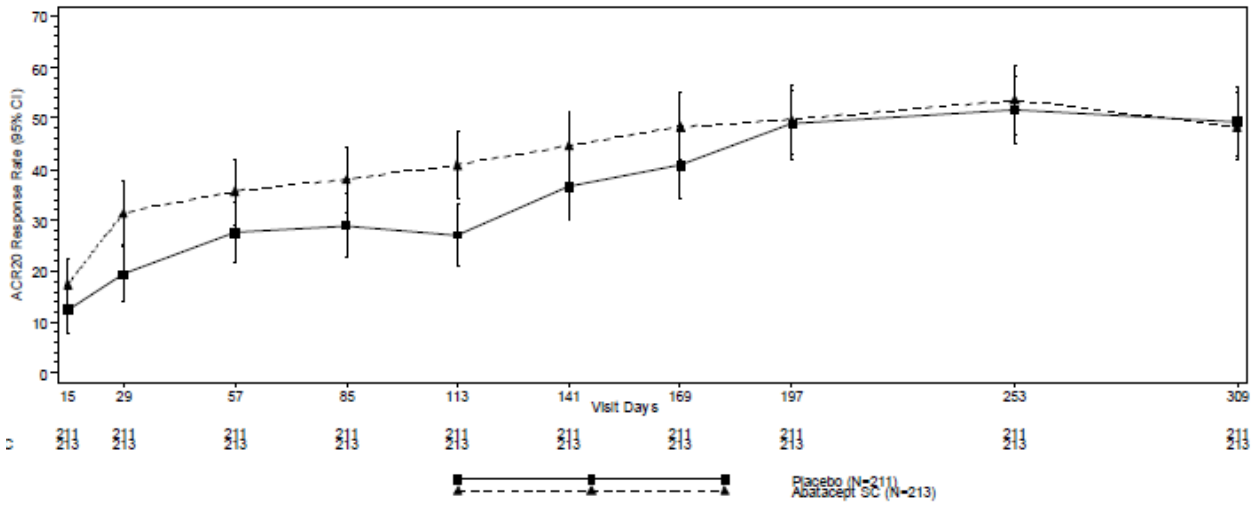

Figure 26 - ACR 20 Response Over Time During Short-term and Open-label Period Combined - ITT Population

Ancillary analyses

No ancillary analyses were conducted.

Summary of main studies

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

Table 44 - Summary of Efficacy for trial IM101158

Title: A Phase IIB, Multi-Dose, Multi-Center, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Abatacept Versus Placebo in the Treatment of Psoriatic Arthritis		
Study identifier	Protocol Number: IM101158 IND Number: BB-IND-9391 EUDRACT Number: 2007-004241-15	
Design	multinational, multi-center, double-blind, multiple dose level, placebo-controlled phase IIB study. The study consisted of 2 study periods: a 6-month double-blind, placebo-controlled short-term (ST) period and an open-label long-term (LT) extension period for subjects who completed the ST period. The primary objective of the short-term period was to compare the efficacy of 3 regimens of abatacept versus placebo in a 6-month double-blind study of PsA, as measured by the proportion of subjects achieving an ACR 20 response at Day 169. The primary objective of the long-term period was to assess the safety and tolerability of abatacept treatment during the open-label extension phase (18 months after the initial 6-month, double-blind period). The long-term period of the study was prematurely terminated due to the modest efficacy on skin-related parameters. *Only the efficacy results of the ST period are presented in this table.*	
	Duration of main phase:	6 months (primary efficacy endpoint at Day 169)
	Duration of Run-in phase:	Screening period
	Duration of Extension phase:	18 months (long-term extension period)

Hypothesis	Superiority (Phase IIb) Abatacept will reduce signs and symptoms of psoriatic arthritis in patients who have had an inadequate response to DMARDs (including, but not limited to, methotrexate or TNFα blockade)		
Treatments groups	Abatacept 30/10		Abatacept 30 mg/kg (by weight) by IV infusion on Days 1 and 15 followed by abatacept (fixed dose) approximating 10 mg/kg on Days 29, 57,85, 113, and 141. Randomized: n=43
	Abatacept 10/10		Abatacept (fixed dose) approximating 10 mg/kg by IV infusion on Days 1, 15, 29, 57, 85, 113, and 141. Randomized: n=40
	Abatacept 3/3		Abatacept 3 mg/kg (by weight) by IV infusion on Days 1, 15, 29, 57, Days 85, 113, and 141. Randomized: n=45
	Placebo		Placebo, IV infusion on Days 1, 15, 29, 57, 85, 113, and 141. Randomized: n=42
Endpoints and definitions (ST)	Primary endpoint	ARC 20	American College of Rheumatology 20% response criteria (ACR20) response rate at Day 169
	Secondary endpoint	IGA	The proportion of subjects with Investigator Global Assessment (IGA) score of clear or almost clear at Day 169
	Secondary endpoint	TL score %	Percentage Improvement from Baseline in Target Lesion (TL) Score at Day 169
	Secondary endpoint	SF-36 PCS	The change from baseline at Day 169 in Short form SF-36 Questionnaire Physical Component Summary Score (PCS)
	Secondary endpoint	SF-36 MCS	The change from baseline at Day 169 in Short form SF-36 Questionnaire Mental Component Summary Score (MCS)
	Secondary endpoint	HAQ Response	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 HAQ-DI score (The Health Assessment Questionnaire (HAQ) disability index (DI))
	Exploratory endpoint	ACR 50	ACR 50% response criteria (ACR50) response rate at Day 169
	Exploratory endpoint	ACR 70	ACR 70% response criteria (ACR70) response rate at Day 169
	Exploratory endpoint	PASI 50	The proportion of subjects achieving a Psoriatic Arthritis Severity Index 50 (PASI 50)
Database lock	Short-term Period Completion Date: 29-Dec-2008 Long-term Period Termination Date: 18-Jan-2011		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat (ITT) **All Randomized and Treated Subjects** **At Day 169**				
Descriptive statistics and estimate variability	Treatment group	Abatacept 30/10	Abatacept 10/10	Abatacept 3/3	Placebo
	Number of subject	43	40	45	42
	ARC20 number of responders, n %	18 41.9%	19 47.5%	15 33.5%	8 19.0%
	95% CI	[27.1, 56.6]	[32.0, 63.0]	[19.6, 47.1]	[7.2, 30.9]

	IGA number of responders, n %	9 20.9%	10 25.0%	17 37.8%	11 26.2%
	95% CI	[8.8, 33.1]	[11.6, 38.4]	[23.6, 51.9]	[12.9, 39.5]
	TL score % Adj. Mean (%) Improvement	19.39%	22.96%	31.11%	0.63%
	SE	(9.16)	(9.46)	(8.98)	(9.35)
	SF-36 PCS Adjusted Mean Change from baseline	7.30	9.27	6.32	0.15
	SE	[1.85]	[1.91]	[1.82]	[1.87]
	SF-36 MCS Adjusted Mean Change from baseline	4.50	4.42	3.16	2.41
	SE	[2.45]	[2.50]	[2.41]	[2.47]
	HAQ Response number of responders, n %	15 34.9%	18 45.0%	16 35.6%	8 19.0%
	95% CI	[20.6, 49.1]	[29.6, 60.4]	[21.6, 49.5]	[7.2, 30.9]
	ACR 50 number of responders, n %	9 20.9%	10 25.0%	7 15.6%	1 2.4%
	95% CI	[8.8, 33.1]	[11.6, 38.4]	[5.0, 26.1]	[-2.2, 7.0]
	ACR 70 number of responders, n %	2 4.7%	5 12.5%	4 8.9%	0
	95% CI	[-1.6, 10.9]	[2.3, 22.7]	[0.6, 17.2]	[0.0, 0.0]
	PASI 50 number of responders, n %	n=20 7 35.0%	n=21 6 28.6%	n=21 9 42.9%	n=21 3 14.3%
	95% CI	[14.1, 55.9]	[9.2, 47.9]	[21.7, 64.0]	[-0.7, 29.3]
Effect estimate per comparison	Primary endpoint **ARC 20**	Comparison groups	Abatacept 30/10 - Placebo	Abatacept 10/10 - Placebo	Abatacept 3/3 - Placebo
		Estimate of Difference[1]	22.9%	28.7%	14.6%
		95% CI	[4.0, 41.8]	[9.4, 48.0]	[-3.5, 32.6]
		P-value	0.022	0.006	0.121
	Secondary endpoint **IGA**	Comparison groups	Abatacept 30/10 - Placebo	Abatacept 10/10 - Placebo	Abatacept 3/3 - Placebo
		Estimate of Difference[1]	-6.0%	-0.5%	10.4%
		95% CI	[-23.0, 11.0]	[-18.0, 17.1]	[-7.6, 28.5]
		P-value	*NR*	*NR*	*NR*
	Secondary endpoint **TL score %**	Comparison groups	Abatacept 30/10 - Placebo	Abatacept 10/10 - Placebo	Abatacept 3/3 - Placebo

		Adjusted difference[2]	18.77%	22.34%	30.48%
		95% CI	[-7.02, 44.56]	[-3.93, 48.60]	[4.82, 56.15]
		P-value	*NR*	*NR*	*NR*
	Secondary endpoint **SF-36 PCS**	Comparison groups	Abatacept 30/10 - Placebo	Abatacept 10/10 - Placebo	Abatacept 3/3 - Placebo
		Adjusted difference[2]	7.15	9.12	6.17
		95% CI	[1.97, 12.33]	[3.83, 14.41]	[1.01, 11.32]
		P-value	*NR*	*NR*	*NR*
	Secondary endpoint **SF-36 MCS**	Comparison groups	Abatacept 30/10 - Placebo	Abatacept 10/10 - Placebo	Abatacept 3/3 - Placebo
		Adjusted difference[2]	2.08	2.01	0.75
		95% CI	[-4.79, 8.96]	[-4.94, 8.95]	[-6.08, 7.58]
		P-value	*NR*	*NR*	*NR*
	Secondary endpoint **HAQ Response**	Comparison groups	Abatacept 30/10 - Placebo	Abatacept 10/10 - Placebo	Abatacept 3/3 - Placebo
		Estimate of Difference[1]	16.0%	26.1%	16.6%
		95% CI	[-2.5, 34.5]	[6.8, 45.5]	[-1.8, 34.9]
		P-value	*NR*	*NR*	*NR*
	Exploratory endpoint **ACR 50**	Comparison groups	Abatacept 30/10 - Placebo	Abatacept 10/10 - Placebo	Abatacept 3/3 - Placebo
		Estimate of Difference[1]	18.4%	22.7%	13.2%
		95% CI	[5.4, 31.5]	[8.6, 36.9]	[1.6, 24.8]
		P-value	*NR*	*NR*	*NR*
	Exploratory endpoint **ACR 70**	Comparison groups	Abatacept 30/10 - Placebo	Abatacept 10/10 - Placebo	Abatacept 3/3 - Placebo
		Estimate of Difference[1]	4.7%	12.5%	8.9%
		95% CI	[-1.6, 11.0]	[2.3, 22.7]	[0.6, 17.2]
		P-value	*NR*	*NR*	*NR*
	Exploratory endpoint **PASI 50**	Comparison groups	Abatacept 30/10 - Placebo	Abatacept 10/10 - Placebo	Abatacept 3/3 - Placebo
		Estimate of Difference[1]	20.7%	14.3%	28.6%
		95% CI	[-10.5, 51.9]	[-15.3, 43.9]	[-3.5, 60.7]
		P-value	*NR*	*NR*	*NR*
Notes	[1] Estimate of difference and p-value are based on Cochran-Mantel-Haenszel method (CMH) with stratification of baseline body surface area (BSA) affected by psoriasis. [2] Adjustment based on ANCOVA model with treatment as factor and baseline value as covariate. Missing values imputed based on last observation carried forward analysis. NR = not reported				

Table 45 - Summary of Efficacy for trial IM101332

Title: A Phase 3 Randomized Placebo Controlled Study to Evaluate the Efficacy and Safety of Abatacept Subcutaneous Injection in Adults with Active Psoriatic Arthritis			
Study identifier	Protocol Number: IM101332 IND Number: BB-IND-9391 EUDRACT Number: 2012-002798-80		
Design	Phase 3, randomized, double-blind, placebo controlled, multicenter study The study included three phases: 24-week (169 days) double-blind, placebo controlled period, followed by a 28-week (196 days) Open label Period and a 52-week Long Term Extension in subjects with 1) active PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR) and 2) active psoriasis defined as having at least one lesion of psoriasis (at least ≥ 2 cm in diameter). On Day 113, subjects who had not achieved a ≥ 20% improvement from baseline (Day 1) in their swollen and tender joint counts were considered treatment failures, removed from their blinded treatment arm, and transitioned to the Early Escape arm in which they received Open-label weekly SC abatacept 125 mg. At Day 169, all subjects transitioned to the Open-label Period and received abatacept 125 mg SC weekly. At the end of Open-label Period, subjects had the option of entering a one-year, Long-term Extension Period for the collection of safety data only. *Only the 24 weeks (169 days) efficacy results are presented in this table.*		
	Duration of main phase:		24 weeks (primary efficacy endpoint at Day 169)
	Duration of Run-in phase:		7-56 days (screening period)
	Duration of Extension phase:		28 weeks (open-label phase) 52 weeks (long-term extension)
Hypothesis	Superiority Abatacept 125 mg when administered SC is more effective than placebo in achieving ACR20 response after 24 weeks (Day 169) of treatment in subjects with active Psoriatic Arthritis (PsA).		
Treatments groups	Abatacept		Abatacept 125 mg, SC, once a week randomized: n=213 number completed period: n=125
	Placebo		Placebo, SC, once a week randomized: n=211 number completed period: n=98
	Early escape patients, n=165 (n=76 (35.7%) from abatacept arm, n=89 (42.2%) from placebo arm)		
Endpoints and definitions (ST)	Primary endpoint	ARC 20	The proportion of ACR 20 responders (American College of Rheumatology 20% response criteria response rate) at Day 169
	Key Secondary endpoint	HAQ Response	The proportion of HAQ responders at Day 169 (a reduction of at least 0.35 from baseline)
	Key Secondary endpoint	ARC 20 TNFi-naive	ACR20 response rate at Day 169 in the subset of subjects who have never been exposed to TNFi therapy
	Key Secondary endpoint	ARC 20 TNFi-exposed	ACR20 response rate at Day 169 in the subset of subjects who have previously taken TNFi therapy
	Key Secondary endpoint	x-ray	Proportion of non-progressors in total PsA-modified Sharp/van der Heidje score (SHS) (defined as a change from baseline in total PsA-modified SHS ≤0) at Day 169

	Secondary endpoint	PASI 50	The proportion of subjects achieving at least 50% improvement from baseline in psoriasis, as assessed by the Psoriatic Arthritis Severity Index 50 (PASI 50) in subjects with baseline BSA ≥ 3%
	Secondary endpoint	ACR 50	ACR 50% response criteria (ACR50) response rate at Day 169
	Secondary endpoint	ACR 70	ACR 70% response criteria (ACR70) response rate at Day 169
	Secondary endpoint	SF-36 PCS	The change from baseline at Day 169 in Short form SF-36 Questionnaire Physical Component Summary Score (PCS)
	Secondary endpoint	SF-36 MCS	The change from baseline at Day 169 in Short form SF-36 Questionnaire Mental Component Summary Score (MCS)
Database lock	5 October 2015 (interim database lock)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) **At Day 169**		
Descriptive statistics and estimate variability	Treatment group	**Abatacept**	**Placebo**
	Number of subjects	213	211
	ARC20 number of responders, n %	 84 39.4%	 47 22.3%
	95% CI	[32.9, 46.0]	[16.7, 27.9]
	HAQ Response number of responders, n %	 66 31.0%	 50 23.7%
	95% CI	[24.8, 37.2]	[18.0, 29.4]
	ARC20 TNFi-naive number of subjects, N number of responders, n %	 84 37 44.0%	 81 18 22.2%
	95% CI	[33.4, 54.7]	[13.2, 31.3]
	ARC20 TNFi-exposed number of subjects, N number of responders, n %	 129 47 36.4%	 130 29 22.3%
	95% CI	[28.1, 44.7]	[15.2, 29.5]
	x-ray number of radiographic non-progressors, n %	 91 42.7%	 69 32.7%
	95% CI	[36.1, 49.4]	[26.4, 39.0]
	PASI 50 number of subjects, N number of responders, n %	 146 39 26.7%	 148 29 19.6%
	95% CI	[19.5, 33.9]	[13.2, 26.0]
	ACR 50 number of responders, n %	 41 19.2%	 26 12.3%
	95% CI	[14.0, 24.5]	[7.9, 16.8]
	ACR 70 number of responders, n %	 22 10.3%	 14 6.6%

	95% CI	[6.2, 14.4]	[3.3, 10.0]
	SF-36 PCS Adjusted Change from baseline SE	 5.11 0.637	 3.69 0.707
	95% CI	[3.86, 6.36]	[2.30, 5.08]
	SF-36 MCS Adjusted Change from baseline SE	 2.56 0.826	 2.62 0.924
	95% CI	[0.93, 4.18]	[0.80, 4.44]
Effect estimate per comparison[1,2]	Primary endpoint **ARC 20**	Comparison groups	Abatacept - Placebo
		Relative risk	1.77
		95% CI	[1.31, 2.39]
		Estimate of Difference[3]	17.2%
		95% CI	[8.7, 25.6]
		P-value[4]	<0.001
	Key Secondary endpoint **HAQ Response**	Comparison groups	Abatacept - Placebo
		Relative risk	1.30
		95% CI	[0.95, 1.79]
		Estimate of Difference[3]	7.2%
		95% CI	[-1.1, 15.6]
		P-value[4]	0.097
	Key Secondary endpoint **ARC20 TNFi-naive**	Comparison groups	Abatacept - Placebo
		Relative risk	1.99
		95% CI	[1.24, 3.20]
		Estimate of Difference[5]	21.9%
		95% CI	[8.3, 35.6]
		P-value (nominal) [6]	0.003
	Key Secondary endpoint **ARC20 TNFi-exposed**	Comparison groups	Abatacept - Placebo
		Estimate of Difference[5]	14.0%
		95% CI	[3.3, 24.8]
		P-value (nominal) [6]	0.012
	Key Secondary endpoint **x-ray**	Comparison groups	Abatacept - Placebo
		Relative risk	1.31
		95% CI	[1.02, 1.68]
		Estimate of Difference[3]	10.0
		95% CI	[1.0, 19.1]
		P-value (nominal) [4]	0.034
	Secondary endpoint **PASI 50**	Comparison groups	Abatacept - Placebo
		Relative risk	1.37
		95% CI	[0.90, 2.09]
		Estimate of Difference[7]	7.3%
		95% CI	[-2.2, 16.7]
	Secondary	Comparison groups	Abatacept - Placebo

	endpoint **ACR 50**	Estimate of Difference[3]	6.9%
		95% CI	[0.1, 13.7]
	Secondary endpoint **ACR 70**	Comparison groups	Abatacept - Placebo
		Estimate of Difference[3]	3.7%
		95% CI	[-1.5, 8.9]
	Secondary endpoint **SF-36 PCS**	Comparison groups	Abatacept - Placebo
		Adjusted Mean Difference[9]	1.42
		95% CI	[-0.32, 3.15]
	Secondary endpoint **SF-36 MCS**	Comparison groups	Abatacept - Placebo
		Adjusted Mean Difference[9]	-0.06
		95% CI	[-2.32, 2.20]

Notes:

[1] Early Escape subjects switching to open-label abatacept at Day 113 and other subjects with missing data at Day 169 of the double-blind period were imputed as non-responders.

[2] Key secondary endpoints were tested in the following hierarchical order, at Day 169:
1) proportion of HAQ responders,
2) proportion of ACR 20 responders in the TNFi-naïve sub-population,
3) proportion of ACR 20 responders in TNF-exposed sub-population,
4) radiographic non-progressor rates as described by the total PsA-modified SHS. Because the treatment difference for HAQ response rate was not significant at the 5% significance level, treatment differences for endpoints lower in the testing hierarchy (ie, ACR 20 response rate at Day 169 in the TNFi-naive and TNFi-exposed cohorts and x-ray non-progressor rate at Day 169) could not be tested at the 5% significance level preserving the type I error. Thus, for these endpoints, nominal p-values and summary statistics are provided.

[3] Estimate and 95% CI for difference is based on stratum size weights method with stratification by MTX use, prior TNFi and BSA.

[4] P-value is based on the CMH Chi-square test stratified by MTX use, prior TNFi and BSA.

[5] Estimate and 95% CI for difference is based on stratum size weights method with stratification by MTX use and BSA.

[6] P-value is based on the CMH Chi-square test stratified by MTX use and BSA.

[7]Estimate and 95% CI for difference is based on stratum size weights method with stratification by MTX use and prior TNF

[8] P-value is based on the CMH Chi-square test stratified by MTX use and prior TNF.

[9] For Early Escape Subjects measurements are set to missing at Day 169. The longitudinal model includes the fixed categorical effects of treatment, day, prior TNFi use, MTX use, BSA, day-by-treatment interaction, prior TNF-use-by-day interaction, MTX use-byday 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.

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

Efficacy Summary

Table 46 summarizes the primary endpoint, ACR 20 response, at Day 169 for both studies.

Table 47 summarizes ACR 20 responses in the LT Period.

Table 48 summarizes ACR 50/70 responses at Day 169.

Table 49 summarizes HAQ responses at Day 169.

Table 50 summarizes PASI 50/75 responses at Day 169.

Table 46 - Proportion of Subjects with ACR 20 Response at Day 169 during the Short-term Period, Study IM101332 (ITT Population) and Study IM101158 (All Randomized and Treated Subjects)

	Study IM101332[a] (Abatacept SC)		Study IM101158[b] (Abatacept IV)			
Primary Endpoint **ACR 20 response**	**Aba N = 213**	**Placebo N = 211**	**Aba 30/10 N = 43**	**Aba 10/10 N = 40**	**Aba 3/3 N = 45**	**Placebo N = 42**
Number of subjects, n/N (%)	84 (39.4)	47 (22.3)	18 (41.9)	19 (47.5)	15 (33.5)	8 (19.0)
95% CI	32.9, 46.0	16.7, 27.9	27.1, 56.6	32.0, 63.0	19.6, 47.1	7.2, 30.9
Estimate of Difference (95% CI)	17.2 (8.7, 25.6)		22.9 (4.0, 41.8)	28.7 (9.4, 48.0)	14.6 (-3.5, 32.6)	N/A
P-value vs placebo	<0.001		0.022	0.006	0.121	N/A

Aba = abatacept.

[a] IM101332: Abatacept 125-mg weekly SC vs placebo SC. Estimate and 95% CI for difference from placebo is based on stratum size weights method with stratification by MTX use, prior TNFi and BSA. P-value is based on the CMH Chi-square test stratified by MTX use, prior TNFi and BSA; 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.

[b] IM101158: Abatacept monthly IV 30/10 mg/kg, 10/10 mg/kg, 3/3 mg/kg, vs placebo IV. Estimate of difference from placebo and p-value are based on Cochran-Mantel-Haenszel method (CMH) with stratification of baseline body surface area (BSA) affected by psoriasis.

Table 47 - Proportion of Subjects with ACR 20 Response During the Open-label/ Long-term Period of Study IM101332 (ITT Population) and Study IM101158 (As-observed Analysis Population in the LT)

	Study IM101332[a] (Abatacept SC)		Study IM101158[b] (Abatacept IV)			
	Day 309		Day 365			
ACR 20 response	**Aba N = 213**	**Placebo N = 211**	**Aba 30/10 N = 34**	**Aba 10/10 N = 29**	**Aba 3/3 N = 36**	**Placebo N = 32**
Number of subjects, n/N (%)	103 (48.4)	104 (49.3)	17 (50.0)	18 (62.1)	22 (61.1)	15 (46.9)
95% CI	41.6, 55.1	42.5, 56.0	33.2, 66.8	44.4, 79.7	45.2, 77.0	29.6, 64.0

Aba = abatacept.-

[a] IM101332: Aba/Placebo indicate treatment groups at randomization.

[b] IM101158: Aba 30/10 mg/kg, 10/10 mg/kg, 3/3 mg/kg, and Placebo indicate treatment groups at randomization.

Table 48 - Proportion of Subjects with ACR 50/70 Response at Day 169 during the Short-term Period, Study IM101332 (ITT Population) and Study IM101158 (All Randomized and Treated Subjects)

	Study IM101332[a] (Abatacept SC)		Study IM101158[b] (Abatacept IV)			
Endpoint	Aba N = 213	Placebo N = 211	Aba 30/10 N = 43	Aba 10/10 N = 40	Aba 3/3 N = 45	Placebo N = 42
ACR 50 response						
Number of subjects, n (%)	41 (19.2)	26 (12.3)	9 (20.9)	10 (25.0)	7 (15.6)	1 (2.4)
95% CI	14.0, 24.5	7.9, 16.8	8.8, 33.1	11.6, 38.4	5.0, 26.1	-2.2, 7.0
Estimate of Difference (95% CI)	6.9 (0.1, 13.7)	N/A	18.4 (5.4, 31.5)	22.7 (8.6, 36.9)	13.2 (1.6, 24.8)	N/A
ACR 70 response						
Number of subjects, n (%)	22 (10.3)	14 (6.6)	2 (4.7)	5 (12.5)	4 (8.9)	0
95% CI	6.2, 14.4	3.3, 10.0	-1.6, 10.9	2.3, 22.7	0.6, 17.2	0.0, 0.0
Estimate of Difference (95% CI)	3.7 (-1.5, 8.9)	N/A	4.7 (-1.6, 11.0)	12.5 (2.3, 22.7)	8.9 (0.6, 17.2)	N/A

Aba = abatacept.
[a] IM101332: Abatacept 125-mg weekly SC vs placebo SC. Early Escape: Imputation as Non-responders at Day 141 and Day 169. Estimate and 95% CI for difference from placebo is based on stratum size weights method with stratification by MTX use, prior TNFi and BSA.
[b] IM101158: Abatacept monthly IV 30/10 mg/kg, 10/10 mg/kg, 3/3 mg/kg, vs placebo IV. Estimate of Difference from placebo and 95% CIs are calculated based on Cochran-Mantel-Haenszel method (CMH) with stratification of baseline body surface area (BSA) affected by psoriasis.

Table 49 - Proportion of Subjects with HAQ Response and Adjusted Mean Change from Baseline in HAQ-DI at Day 169 during the Short-term Period, Study IM101332 (ITT Population) and Study IM101158 (All Randomized and Treated Subjects)

	Study IM101332[a] (Abatacept SC)		Study IM101158[b] (Abatacept IV)			
Endpoint	Aba	Placebo	Aba 30/10	Aba 10/10	Aba 3/3	Placebo
HAQ response, n	**213**	**211**	**43**	**40**	**45**	**42**
Number of subjects, n (%)	66 (31.0)	50 (23.7)	15 (34.9)	18 (45.0)	16 (35.6)	8 (19.0)
95% CI	24.8, 37.2	18.0, 29.4	20.6, 49.	29.6, 60.4	21.6, 49.5	7.2, 30.9
Estimate of Difference (95% CI)	7.2 (-1.1, 15.6)		16.0 (-2.5, 34.5)	26.1 (6.8, 45.5)	16.6 (-1.8, 34.9)	N/A
P-value	0.097		N/A	N/A	N/A	N/A
Adjusted Mean Change from Baseline, n	**124[c]**	**98[c]**	**43**	**40**	**44**	**41**
Mean change from BL (SE)	-0.33 (0.04)	-0.20 (0.05)	-0.28 (0.08)	-0.40 (0.08)	-0.29 (0.07)	0.04 (0.08)
95% CI	-0.41, -0.24	-0.29, -0.10	N/A	N/A	N/A	N/A
Adjusted Difference in Mean change (95% CI)	-0.13 (-0.25, -0.01)	N/A	-0.32 (-0.53, -0.1)	-0.44 (-0.65, -0.22)	-0.33 (-0.54, -0.11)	N/A

Aba = abatacept; N/A = not available or not applicable; BL = baseline.
[a] IM101332: Abatacept 125-mg weekly SC vs placebo SC. HAQ Response is defined as an improvement of at least 0.35 units from baseline. P-value is based on the CMH Chi-square test stratified by MTX use, prior TNFi and BSA. Estimate and 95% CI for difference from placebo is based on stratum size weights method with stratification by MTX use, prior TNFi and BSA. Early Escape subjects switching to open-label abatacept at Day 113 and subjects with missing data at Day 169 of the double-blind period were imputed as non-responders. For change from baseline: for Early Escape Subjects measurements are set to missing at Day 141 and Day 169.
[b] IM101158: Abatacept monthly IV 30/10 mg/kg, 10/10 mg/kg, 3/3 mg/kg, vs placebo IV. HAQ response is defined as an improvement of at least 0.3 unit from baseline in the HAQ Disability Index. Estimate of Difference from placebo and 95% CIs are calculated based on Cochran-Mantel-Haenszel method (CMH) with stratification of baseline body surface area (BSA) affected by psoriasis. For change from baseline: Adjustment based on ANCOVA model with treatment as factor and baseline value as covariate (LOCF analysis).
[c] N is number of subjects with both post-baseline and baseline measurements at Day 169 double-blind. Estimates are based on a longitudinal analysis including all timepoints and all subjects in ITT population.

Table 50 - Proportion of Subjects (with BSA>=3%) Achieving PASI 50/75 at Day 169, Study IM101332 (ITT Population) and Study IM101158 (All Randomized and Treated Subjects)

	Study IM101332[a] (Abatacept SC)		Study IM101158[b] (Abatacept IV)			
Endpoint	Aba	Placebo	Aba 30/10	Aba 10/10	Aba 3/3	Placebo
PASI 50 response, n	**146**	**148**	**20**	**21**	**21**	**21**
Number of subjects, n (%)	39 (26.7)	29 (19.6)	7 (35.0)	6 (28.6)	9 (42.9)	3 (14.3)
95% CI	19.5, 33.9	13.2, 26.0	14.1, 55.9	9.2, 47.9	21.7, 64.0	-0.7, 29.3
Estimate of Difference (95% CI)	7.3 (-2.2, 16.7)[c]		20.7 (-10.5, 51.9)	14.3 (-15.3, 43.9)	28.6 (-3.5, 60.7)	N/A
PASI 75 response, n	**146**	**148**	**20**	**21**	**21**	**21**
Number of subjects, n (%)	24 (16.4)	15 (10.1)	2 (10.0)	3 (14.3)	8 (38.1)	1 (4.8)
95% CI	10.4, 22.5	5.3, 15.0	-3.1, 23.1	-0.7, 29.3	17.3, 58.9	-4.3, 13.9
Estimate of Difference (95% CI)	6.4 (-1.3, 14.1)		5.2 (-15.6, 26.1)	9.5 (-13.0, 32.0)	33.3 (3.8, 62.9)	N/A

Aba = abatacept; N/A = not applicable or not available.
[a] IM101332: Abatacept 125-mg weekly SC vs placebo SC. PASI 50/75: Estimate and 95% CI for difference is based on stratum size weights method with stratification by MTX use and prior TNF. Early Escape Subjects: Imputation as Non-responders at Day 141 and Day 169.
[b] IM101158: Abatacept monthly IV 30/10 mg/kg, 10/10 mg/kg, 3/3 mg/kg, vs placebo IV.
[c] P-value = 0.137, based on the CMH Chi-square test stratified by MTX use and prior TNF.

Clinical studies in special populations

No clinical studies in special populations were conducted which was considered acceptable by CHMP.

Supportive studies

No clinical studies in special populations were conducted which was considered acceptable by CHMP.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Two clinical studies in PsA were submitted to support this application: a phase 2b study of IV abatacept (IM101158) and a pivotal Phase 3 study of SC abatacept (IM101332)

Based on predicted median trough levels (see Clinical Pharmacology section) and prior experiences from RA and psoriasis studies, three IV dose regimens were studied in the Phase 2b study (3 mg/kg, 10 mg/kg, and 10 mg/kg with loading doses of 30 mg/kg on Days 1 and 15). For the phase 3 study, a fixed dose approved for RA, i.e., abatacept 125 mg SC weekly was selected, based on comparable exposure following administration of 10 mg/kg IV abatacept in RA and PsA patients. The exposure-response relationship was extrapolated from RA to PsA. It was clarified that the aim of the initial doses of i.v. 2x30 mg/kg in the third dose group was to investigate whether higher doses were needed to saturate target molecules in PsA. Higher than 30/30/10 mg/kg dose regimens were not investigated.

Study IM101158

The Phase 2 b Study IM101158 consisted of two study periods: a 6-month double-blind, placebo-controlled short term period and an open-label long term extension period of 18 months. The study population comprised adult patients who met CASPAR criteria of PsA, with active disease (≥ 3 swollen joints and ≥ 3 tender joints), and ≥ 1 psoriatic skin lesion ≥ 2 cm. Patients exhibited prior failure of DMARD therapy (lack of efficacy or intolerability). Prior failure of TNFα therapy was also allowed. Concomitant treatment with stable dose of MTX, NSAID, oral corticosteroids (≤10 mg daily prednisone equivalent) and topical corticosteroids (for groin, face, and/or hands) was permitted.

Subjects were randomized on Day 1 and received one of the following four treatments by IV infusion during the ST period: Abatacept 30/10 mg/kg, abatacept 10/10 mg/kg, abatacept 3/3 mg/kg or Placebo. Subjects who entered the LT period received open-label treatment with abatacept at 10 mg/kg beginning at Day 169.

The primary objective was to compare the efficacy of the three regimens of abatacept versus placebo in the 6-month double-blind period, as measured by the proportion of subjects achieving an ACR 20 response at Day 169. Efficacy endpoints included ACR 20 response, IGA response, target lesion score (defined as a score of clear or almost clear in all 3 components: Induration, Erythema, Scaling; rating 0-4 each), physical and mental component score of SF-36, and HAQ response. All these endpoints are validated and/or standard endpoints for studies in PsA and psoriasis. Mean changes from baseline in bone erosions, bone oedema, synovial volume, dactylitis and enthesitis by MRI was assessed as an exploratory endpoint at Day 365 (LT Period).

The efficacy analyses for the double-blind ST period were performed using the Intent-to-treat (ITT) analysis population, and analyses of efficacy and safety endpoints for the LT period were based on the As Treated Subjects analysis population. According to the statistical analysis plan, missing scores during the ST period were imputed as non-responders for ACR, IGA, HAQ, PASI, and target lesion responses, and missing target lesion scores at Day 169 were imputed using a last observation carried forward (LOCF).

Study IM101332

The pivotal study IM101332 was a 24-week (169 days), Phase 3, randomized, double-blind, placebo controlled, multicentre study, followed by a 28-week (196 days) Open-label Period and a 52-week Long-Term Extension. Similar to Study IM101158, the population included patients who met CASPAR criteria of PsA, with active disease (≥ 3 swollen joints and ≥ 3 tender joints), and ≥ 1 psoriatic skin lesion ≥ 2 cm. Patients had a history of inadequate response to at least one non-biologic DMARD and could have been treated with TNFi therapy. Those who had failed more than 2 TNFi agents due to inefficacy were excluded but there was no limit on the total number of TNFi to which the subject had been exposed.

Concurrent treatment with stable dose of non-biologic DMARD, NSAID, oral glucocorticoid (doses ≤ 10 mg/day prednisone), low potency topical corticosteroids (for palms, soles, face and intertriginous areas) and systemic retinoid was allowed. One instance of rescue therapy with corticosteroid (oral, IM, IA, enthesial injection or topical) was permitted during the ST period.

Study subjects received either abatacept 125 mg SC or placebo SC once per week during the blinded period of the first 6 months. There was an early escape and transition to open-label abatacept treatment on Day 113 (Week 16) for those who not who did not achieve a ≥ 20% improvement in their swollen and tender joint count. These subjects were considered treatment failures.

The primary objective of the study was to compare the efficacy of abatacept to placebo as assessed by the ACR 20 response at Day 169. The primary endpoint was the proportion of ACR 20 responders at Day 169. This is a standard efficacy endpoint in PsA studies and in line with the EMA guidance

(CHMP/EWP/438/04). Proportion of HAQ responders, proportion of ACR 20 responders in the TNFi-naïve and the TNFi-exposed subpopulation, and proportion of x-ray non-progressors in total PsA-modified SHS were chosen as key secondary endpoints. ACR50 and 70 response, skin specific endpoint PASI 50, and physical and mental function subscales of the SF-36 were included as other secondary endpoints. These endpoints are validated and widely used for studies in PsA. Exploratory endpoints included composite measures of disease activity including CPDAI and PASDAS, and endpoints measuring spinal symptoms, enthesitis and dactylitis including BASDAI, LEI and LDI-Basic. Day 365 (Year 1/Open-label [OL] Day 197) efficacy assessments were exploratory.

The planned sample size was 400 randomized subjects (200 per arm). The sample size calculation was based on > 99% power to detect a treatment effect in ACR 20 responder rate between the abatacept arm (41%) and the placebo arm (18%) at Day 169 at the 5% significance level, and at least 80% for each of the endpoints included in the hierarchical testing procedure, and for the skin endpoint PASI 50. Standard measures for randomization and blinding were used. Randomization was stratified globally by current MTX use, prior use of TNFi therapy, and psoriasis involving ≥ 3% of the BSA. Up to approximately 40% of subjects with < 3% BSA psoriatic skin involvement were planned to be randomized.

Efficacy analyses were performed using the ITT analysis population. Formal statistical testing with Cochran-Mantel Haenszel Chi-Squared test was conducted for the primary and the key secondary efficacy endpoints using a hierarchical approach, with statistically significance at α= 5%. Early escape subjects were imputed as non-responders at Days 141 and 169. Additional analyses were provided using the observed data from Open-label Day 29 and Day 57.

Efficacy data and additional analyses

Study IM101158

Of the 170 randomized and treated subjects in Study IM101158, 147 subjects completed the ST period, each of whom entered the LT period. There were no clinically relevant differences in the proportion of subjects discontinued for a specific reason among the treatment groups. Despite the long duration of 6 months (169 days) of the placebo-controlled phase, 78.6% (33 out of 42) of the placebo-treated patients completed the period. In the LT period, 52% of the subjects were discontinued due to premature termination of the study (due to modest efficacy on skin-related parameters), and approximately one third in each treatment group were discontinued due to lack of efficacy. The mean (SD) number of months of exposure among the 147 subjects in the LT Period population was 17.8 (9.09 months).

The treatment groups were balanced with respect to demographic characteristics and baseline disease characteristics. Most subjects were from North America (57.1%) or Europe (30.6%). The mean tender and swollen joint count at baseline was 22.2 and 10.9, respectively. 49% of the study population had BSA ≥ 3%. The mean IGA score was 2.5 (score range from 0=clear to 4=severe) and the mean PASI score was 12.6 (median 8.6) overall indicating mild or moderate skin disease. The patients had prior failure of DMARD therapy due to inefficacy or intolerance. 69.0% to 85.0% of subjects across the four treatment groups had a history of MTX use and 21.4% to 27.5% had a history of DMARD therapy other than MTX prior to enrolment. Overall, 37.1% had a history of inefficacy or intolerance to anti-TNF biologicals (51.2% in abatacept 30/10 mg/kg group; 32.5% in abatacept 10/10 mg/kg group, 35.6% in abatacept 3/3 mg/kg group, and 28.6% in placebo group). The high number of TNF IR patients in the abatacept 30/10 mg/kg group may have lead to underestimation of efficacy in this dose group, while the number TNF IR patients in the other dose groups was comparable. At enrollment, approximately 60% of subjects in each treatment group were receiving MTX, and 19.0% to 27.5% received corticosteroids.

The primary efficacy endpoint ACR 20 response rate at Day 169 was similar for abatacept 30/10 mg/kg (41.9%) and abatacept 10/10 mg/kg (47.5%) treatment groups and significantly higher in comparison to placebo group (19.0%; p = 0.022 and 0.006, respectively).

Among the secondary efficacy endpoints related to PsA, subjects treated with abatacept demonstrated greater improvement at Day 169 in the physical component of SF-36 in comparison to subjects treated with placebo, with the highest adjusted differences from placebo of 9.12 in the abatacept 10/10 mg/kg group. The 95% CIs for each comparison to placebo did not contain zero. Some improvement was also seen in the mental component of SF-36 but all 95% CIs for the adjusted differences contained zero. The estimated differences from placebo in the HAQ-DI scores were 16.0%, 26.1%, and 16.6% for the abatacept 30/10 mg/kg, 10/10 mg/kg, and 3/3 mg/kg groups, respectively, and for the abatacept 10/10 mg/kg group the 95% CI did not contain zero.

The secondary efficacy endpoints related to skin disease (psoriasis) were IGA score and target lesion score at Day 169. The results related to these endpoints were inconclusive as neither difference to placebo nor dose-response in the abatacept groups was evident. This may partly be related to the choice of the endpoints, as some trend in favor of efficacy of abatacept was seen in PASI 50 and PASI 75 responses (see *Analysis performed across trials*). The potential effect of the chosen skin-related secondary endpoints in Study IM101158 was further discussed and it was concluded that, the endpoints and their sensitivity in mild-to-moderate psoriasis may play some role in the skin-related efficacy results.

Among exploratory efficacy endpoints, changes from baseline in MRI results for erosion, edema, synovitis, dactylitis, and enthesitis at Day 169 showed a consistent trend of efficacy of abatacept compared to placebo.

In a post-hoc analysis of ACR 20 and ACR 50 response rates among subjects with prior exposure to TNFi and TNFi-naive subjects, lower responses were observed in the TNFi-exposed subgroup, as expected. The ACR 20 responses with abatacept 10/10 mg/kg dose in the TNFi-exposed and the TNFi-naive subgroups were 30.8% and 55.6%, respectively (for the latter comparison the 95% CI did not overlap with that of placebo). The corresponding ACR 50 responses were 15.4% and 29.6%, respectively. In the other dose groups there was also a consistent numerical trend in favour of abatacept in both TNFi subgroups. However, the 95% CIs were wide and partly overlapping with those of placebo, due to the modest efficacy and the small number of subjects in each subgroup.

During the LT period, all subjects were treated with open-label 10/10 mg/kg abatacept and efficacy data are described at Days 365 and 729 (Months 6 and 18 of LT period, i.e., Months 12 and 24 of the study). There were a decreasing number of subjects at the later time points due to the premature termination of the study due to the modest efficacy on skin-related parameters. Also, one third of subjects discontinued due to lack of efficacy. As a result of this high rate of discontinuation due to lack of efficacy and the as-observed analysis, the response rates become higher. The choice of the abatacept 10/10 dose was further justified in response to the RSI. The simulated and the observed probability of ACR 20 versus Cminss showed that 125 mg SC weekly and 10 mg/kg IV monthly regimens provide similar ACR 20 responses. During the LT period, when all subjects received 10 mg/kg IV abatacept, patients initially randomized to the abatacept 30/10 and 10/10 groups maintained their ACR 20 responses based on the protocol specified as-observed analysis. Similar results were obtained when subjects who discontinued due to lack of efficacy were imputed as non-responders. There was no additional benefit of the higher abatacept 30/10 dose over the 10/10 dose. It is therefore concluded that abatacept 10/10 mg/kg dose is the most optimal one. Results of the skin-related endpoints remained inconclusive. However, subjects who had been treated with placebo in the ST period showed some improvement in both joint- and skin-related efficacy endpoints following switch to the abatacept 10/10 mg/kg dose.

Taken together, based on Study IM101158, IV abatacept has modest efficacy in PsA. Among the doses tested, abatacept 10/10 mg/kg dose that is approved for the treatment of RA was the most effective. The results of the skin-related endpoints IGA and target lesion score assessed as key secondary efficacy endpoints showed no relevant difference to placebo and no dose-response.

Study IM101332

In Study IM101332, 424 subjects were randomized (abatacept n = 213 and placebo n = 211) and received at least one dose of double-blind study drug. 76 (35.7%) of subjects in the abatacept group and 89 (42.2%) of subjects in the placebo group were designated as Early Escape and transitioned to the OL Period at Day 113. Overall, 81 (38.0%) of subjects in the abatacept group discontinued due to lack of efficacy during the Short-term Period which is a high rate of non-responders for an active treatment arm. The vast majority of those withdrawn due to inefficacy showed lack of joint improvement (lack of joint or lack of joint+ skin efficacy).

These patients were imputed as non-responders in the efficacy analysis. 382 subjects entered the OL Period (abatacept n = 197 and placebo n = 185). 14.4% of subjects discontinued the OL Period, most of whom due to the lack of efficacy (9.6% of subjects in the abatacept group and 5.4% of subjects in the placebo group).

Baseline disease characteristics were similar between the treatment groups. Among stratification factors, overall, 60% of subjects were currently using MTX, 61% of subjects had previous exposure to TNFi, and 31% of subjects had < 3% BSA psoriatic skin involvement. Prior and concomitant anti-rheumatic therapy was similar in both groups and baseline MTX dose was 17.1 mg weekly. The mean tender and swollen joint count at baseline was 20.2 and 11.6, respectively, and the mean PASI score was 7.3 (median 4.5) indicating mild psoriasis.

129 (60.6%) subjects in the abatacept group and 130 (61.6%) subjects in the placebo group had prior TNFi therapy. 16.5% and 18.0% of the TNFi-exposed subjects, respectively, were exposed to more than one prior TNFi therapy. Subjects must have had inadequate response to non-biologic DMARD and despite this, 60% of patients were maintained on MTX. The reasons are unclear. 60% of subjects had been previously exposed to biologic DMARD, 40% were biologics-naïve. A substantial proportion of patients who failed to TNFi therapy (18% -aba, 20%-pbo) had failure for unknown reasons. According to CSR, almost all subjects received prior non biologic DMARD (98%), the vast majority received MTX (91-94%) and 13-19% received leflunomide. Other non-biologic DMARD exposure was negligible.

Significantly higher proportion of subjects in the abatacept group compared to the placebo group met the ACR 20 response criteria at Day 169 (39.4% vs. 22.3%, respectively, p <0.001). Among subgroups analyses, the proportion of subjects with an ACR 20 response was numerically higher in patients who used MTX or non-biological DMARD at baseline. In patients with MTX use at Day 1, 44.2% achieved ACR 20 response versus 32.1% of those with no MTX use at baseline.

Among the key secondary endpoints, the proportion of HAQ responders was numerically higher in the abatacept group compared to the placebo group but was not statistically significant (31.0% vs. 23.7%, respectively, p=0.097). Since the analysis of HAQ-response showed statistically non-significant result, treatment differences for endpoints lower in the testing hierarchy (i.e., ACR 20 response rate at Day 169 in the TNFi-naive and the TNFi-exposed cohorts and x-ray non-progressor rate at Day 169) could not be tested for significance. Consequently, statistical claims for the presented nominal p-values cannot be made.

Higher proportion of subjects in the abatacept group met the ACR 20 response criteria at Day 169 in both the TNFi-naive and TNFi-exposed subpopulations (44.0% and 36.4%, respectively) compared to the

placebo group (22.2% and 22.3%, respectively; nominal p-values 0.003 and 0.012, respectively; and the 95% CIs for the estimates of difference did not contain zero).

There was also a higher proportion of radiographic non-progressors at Day 169 in the abatacept group compared to the placebo group (42.7% vs. 32.7%; nominal p-value=0.034; the 95% CI for the estimate of difference did not contain zero). However, the adjusted mean change from baseline in the total SHS was slightly higher in the abatacept group compared to the placebo group at Day 169 (0.48 vs. 0.36). The mean change was overall low (< 0.5, i.e., below the minimal clinically important difference) and the 95% CIs of mean change were overlapping (abatacept 0.48 [0.15, 0.81]; placebo 0.36 [-0.03, 0.75]). Also, the median change from baseline was numerically lower in the abatacept group (0.04) than in the placebo group (0.15). Following longer treatment duration of 1 year, the mean changes from baseline in the abatacept group were numerically lower both at Day 169 (0.30) and Day 365 (0.18), compared to the placebo / placebo-abatacept group (Day 169: 0.35 and Day 365: 0.30).

6 months is a relatively short period to assess progression of structural damage in PsA and the results are confounded by the placebo-treated subjects who escaped to the active drug. However, based on the data available up to one year, it can be concluded that abatacept treatment has a beneficial effect on joint structure.

Among the other secondary endpoints, 26.7% of the abatacept-treated subjects achieved PASI 50 at Day 169 compared to 19.6% of the placebo-treated subjects (p-value=0.137). This outcome was neither clinically nor statistically significant. Higher proportion of abatacept-treated patients met the ACR 50 response criteria compared to the placebo group (19.2% vs. 12.3%, respectively). There was also a trend of better efficacy of abatacept regarding ACR 70 response at Day 169 (10.3% vs. 6.6%, respectively, the 95% CI for the estimate of difference to placebo however contained zero).

Comparisons to placebo of ACR 50 and ACR 70 responses by prior TNFi use also showed a trend of better efficacy of abatacept but all 95% CIs for the estimates of difference to placebo contained zero. The magnitude of effect on skin outcomes is far from the efficacy results of other systemic antipsoriatic agents either measured in plaque psoriasis or in PsA-studies. Further, subjects in the abatacept group showed a trend of improvement in the physical component of SF-36 while change in the mental component of SF-36 was similar to the placebo group. Exploratory assessments related to composite measures of disease activity (CPDAI and PASDAS), enthesitis, dactylitis and axial symptoms (BASDAI) at Day 169 showed a trend of improvement in the abatacept group but with small difference to the placebo group.

Among the exploratory endpoints up to one year (OL Period), the ACR 20/50/70 and PASI 50/70 responses were maintained or slightly higher compared to Day 169, and similar between the aba/aba and the placebo/aba groups. The proportion of radiographic non-progressors in total SHS was 52.6% and 54.5%, respectively, and the adjusted mean change from baseline was 0.18 and 0.30, respectively.

The effect was more pronounced in the IV study IM101158. This is likely to be due to the small number of patients in Study IM101158 leading to large variability, and due to the fact that in the IV study no early escape was possible. Also, the patient populations were different in the two studies: Study 1332 included around 60% TNFi-IR, while the IV study included less than 40% TNFi-IR subjects. Taking these issues into account it can be concluded that IV and SC abatacept have similar and clinically relevant level of efficacy in the treatment of PsA.

2.4.4. Conclusions on the clinical efficacy

The phase 2b study of IV abatacept (IM101158) and the pivotal phase 3 study of SC abatacept (IM101332) included subjects with PsA and psoriasis. The proportion of subjects exposed to prior TNFi

therapy was 37.1% in Study M101158 and 61.1% in Study IM101332, and 17.2% of the subjects in the latter study were exposed to more than one prior TNFi therapy. The proportion of subjects taking MTX at baseline was approximately 60% in all treatment groups.

The primary efficacy endpoint was achieved in both studies, as significantly higher proportion of abatacept-treated subjects compared to placebo-treated subjects met the ACR 20 response criteria at Day 169: 47.5% in the IV abatacept 10/10 mg/kg dose group vs. 19.0% in the placebo-group (p=0.006) and 39.4% in the SC abatacept group vs. 22.3% in the placebo-group (p <0.001). Despite having met the primary endpoint, the magnitude of effect both in absolute terms and relative to placebo is modest.

The lack of active control has been appropriately justified by the high proportion of subjects who had already failed a TNFi, thereby precluding the use of TNFi as a comparator. Also at the time of initiation of the study there were no other approved biological or new non-biological DMARDs.

Results of the secondary efficacy endpoints related to signs and symptoms of PsA only partially supported the primary efficacy analysis. However, in the long term treatment up to one year, the effects of IV and SC abatacept were maintained.

The population, particularly in study IM101332, was rather treatment resistant as 61.1% of subjects had previous exposure to TNFi. The efficacy based on ACR 20 response in this subpopulation was demonstrated but was lower than in the TNFi-naive population.

Abatacept is used only in combination with MTX in the treatment of the other approved indications RA and JIA. It was explained that subjects in both abatacept studies continued receiving non-biologic DMARDs (including MTX) if the investigator believed there was some evidence of efficacy in joints and/or skin (partial response) but add-on therapy with another agent was needed. Abatacept monotherapy group included subjects who had discontinued non-biologic DMARDs such as MTX due to failure or intolerance prior to the trial. The available data suggest that concomitant therapy with non-biologic DMARD, in particular with MTX, provides some additional efficacy over monotherapy and the safety of such therapy is acceptable. On the other hand, efficacy of abatacept monotherapy is not outstanding but a clear difference to placebo can be observed. Therefore, treatment with or without MTX is considered acceptable. As such, Orencia can be used either alone or in combination with MTX for the treatment of PsA. Data on treatment with or without nbDMARD are too limited to allow such recommendation.

The mean PASI scores in Studies IM101158 and IM101332 were 12.6 and 7.3 (median scores 8.6 and 4.5), respectively, indicating mild to moderate psoriasis. There was no clinically relevant effect of abatacept on skin symptoms. Confidence intervals overlapped between placebo and abatacept groups in PASI50, PASI75 parameters and nail-VAS; suggesting that the numerically better results may be not interpreted as real difference (however, the study was not powered for it). Abatacept therapy does also not allow concurrent treatment of psoriasis with effective biological products currently available and indicated for the treatment of both PsA and psoriasis. Therefore abatacept seems unsuitable for the treatment of PsA in patients with moderate to severe psoriasis and patients that require additional systemic therapy for psoriasis were excluded from the indication.

The robustness of the efficacy data and the proposed target population was further justified. Efficacy of abatacept by prior and concomitant MTX was sufficiently demonstrated but the data related to the treatment with or withour MTX were not fully consistent. ACR 20 responses in the subgroups by prior TNFi exposure, with or without MTX, consistently showed improvement relative to placebo, and higher response rates in the anti-TNF naïve patients were seen. Again, responder rates by concomitant MTX were not consistent.

Finally, with regard to the target population, it is concluded that benefit of IV and SC abatacept has been demonstrated in PsA population in both second-line (DMARD-IR) and third-line (TNFi-IR) treatment. The efficacy was clinically relevant but rather modest which is partly explained by the relatively slow onset of action of abatacept in PsA patients and the design of Study IM101332 with early and stringent escape option.

2.5. Clinical safety

Introduction

Orencia (abatacept) administered intravenously (IV) or subcutaneously (SC) is approved for the treatment of rheumatoid arthritis (RA) in adults. Abatacept IV is also approved for the treatment of polyarticular juvenile idiopathic arthritis (JIA) in pediatric patients 6 years of age and older. The safety profile of abatacept is well established for adults with RA, including long-term follow-up. The safety profile is characterised by several potentially serious consequences, including but not limited to the identified risk of infections and potential risks of malignancies, autoimmune disorders, local injection site reactions and immunogenicity, which were also monitored during the clinical studies in psoriatic arthritis (PsA).

The safety data for patients with active PsA is derived from 2 clinical studies: IM101332, a pivotal Phase 3 study of SC abatacept and IM101158, a Phase 2b study of IV abatacept. A total of 594 subjects with active PsA were treated in the 2 clinical studies; 341 subjects received abatacept and 253 subjects received placebo during the ST period. After the ST period, all subjects received open-label (OL) abatacept in order to assess the long term safety of abatacept in subjects with PsA. Study IM101158 was terminated prematurely by the MAH due to the modest efficacy in skin-related parameters. Safety data are presented separately for each study. No formal comparison of safety data were made between treatments or between studies and no formal statistical testing was performed.

Adverse events are further discussed by categories of AEs that could be associated with the use of immunomodulatory drugs. These AEs of special interest include infections, malignancies, autoimmune events, injection site reactions [IM101332], infusion reactions [IM101158], and AEs occurring within 24 hours of study drug administration (IM101332). Autoimmune events, local injection site reactions, acute and peri-infusional reactions were pre-specified.

Patient exposure

As of 22-Dec-2015, 10,771 subjects have been exposed to abatacept in sponsored clinical trials. The cumulative number of patients treated as of 30-Sep-2015 is estimated to be 383,451.

Study IM101158

The median duration of exposure to study drug in the ST period was 168 days for each of the treatment group and the mean duration of exposure in the ranged from 153.6 to 166.8 days.

The mean (SD) number of months of exposure among the 147 subjects in the All Treated Subjects in LT Period population was 17.8 (9.09 months) and the overall mean duration of exposure for the 161 subjects across ST + LT periods was 20.4 (10.74 months) and the mean number (SD) of infusions was 21.3 (11.03).

Study IM101332

The mean durations of exposure to abatacept and to placebo were similar. A total of 46% of subjects in the abatacept group and 36% of subjects in the placebo group were exposed to study drug for › 141 to 169 days, and the median days (SD) of exposure was 147.7 days (30.5) and 140.3 days (30.0), respectively.

In the period up to Year 1, the mean duration of exposure to abatacept was 10.8 months in subjects who received abatacept during the ST and OL Periods and 6.5 months in subjects who received placebo during the ST Period and transitioned to abatacept in the OL Period and the mean number of injections were 43.5 and 26.0, respectively. According to MAH, the mean number of abatacept injections for each group was consistent with the design of this study. Up to Year 2, the mean duration of exposure to abatacept was 17.0 months for the cumulative abatacept period, and the mean number of injections 63.2.

Adverse events

Adverse events were reported in comparable proportions of subjects treated with abatacept and placebo during the Short-term Periods in Studies IM101332 and IM101158 (see Table 51). In study IM101132 during the cumulative abatacept up to Year 1, AEs were reported in 68.6% of subjects and up to Year 2, AEs were reported in 78.4% of subjects. In study IM101158, for all abatacept treated population, AEs were reported 88.8% of the subjects. Infections were the most common types of AEs reported with abatacept therapy and were reported similarly in both abatacept and placebo groups.

No new or unexpected safety signals were identified with abatacept therapy and the AE profile of abatacept administered SC or IV in subjects with PsA was consistent with the AE profile of abatacept observed from the clinical experience of abatacept administered SC or IV in subjects with RA.

The following AEs were considered to be of special interest and are further presented below: infections, malignancies, autoimmune events, local site reactions, acute infusion reactions, peri-infusional reactions and AEs within 24 h of injection are discussed separately.

Table 51 - Adverse Event Summary for Short-Term Period, IM101332 and IM101158-As-Treated Populations

	IM101332		**IM101158**			
	Abatacept SC (N=213)	**Placebo SC (N=211)**	**Abatacept 30/10 IV (N=43)**	**Abatacept 10/10 IV (N=40)**	**Abatacept 3/3 IV (N=45)**	**Placebo IV (N=42)**
Deaths	0	0	0	0	0	0
SAEs	6 (2.8)	9 (4.3)	4 (9.3)	2 (5.0)	0	1 (2.4)
Treatment-Related SAEs[a]	1 (0.5)	1 (0.5)	1 (2.3)	1 (2.5)	0	0
Discontinued due to SAEs[b]	3 (1.4)	3 (1.4)	1 (2.3)	0	0	0
AEs	116 (54.5)	112 (53.1)	29 (67.4)	31 (77.5)	31 (68.9)	30 (71.4)
Treatment-Related AEs	33 (15.5)	24 (11.4)	13 (30.2)	13 (32.5)	12 (26.7)	7 (16.7)
Discontinued due to AEs[c]	3 (1.4)	4 (1.9)	1 (2.3)	2 (5.0)	1 (2.2)	3 (7.1)
Discontin. due to AEs of Infection[d]	3 (1.4)	0	1 (2.3)	0	0	0
AEs of Special Interest						
Infections	57 (26.8)	63 (29.9)	15 (34.9)	14 (35.0)	16 (35.6)	15 (35.7)
Malignancies[e]	0	2 (0.9)	1 (2.3)	0	0	0

	IM101332		IM101158			
	Abatacept SC (N=213)	**Placebo SC (N=211)**	**Abatacept 30/10 IV (N=43)**	**Abatacept 10/10 IV (N=40)**	**Abatacept 3/3 IV (N=45)**	**Placebo IV (N=42)**
Autoimmune Events	0	0	0	3 (7.5)	0	1 (2.4)
Local Injection Site Reactions	1 (0.5)	1 (0.5)	NA	NA	NA	NA
Acute Infusion Reactions	NA	NA	2 (4.7)	2 (5.0)	0	0
Peri-infusional Reactions	NA	NA	4 (9.3)	6 (15.0)	3 (6.7)	3 (7.1)
AEs within 24 hr of Injection	39 (18.3)	39 (18.5)	NE	NE	NE	NE

[a] IM101332: *Pneumocystis jirovecii* infection (abatacept) and ALT increased (PBO); IM101158: osteomyelitis (30/10 mg/kg) and gastroenteritis (10/10 mg/kg)

[b] IM101332: *Pneumocystis jirovecii* infection, gastroenteritis, interstitial lung disease (with an AE of respiratory tract infection) in the abatacept group and invasive ductal breast carcinoma, B-cell lymphoma, and ALT increased in the PBO group; IM101158: osteomyelitis (30/10 mg/kg)

[c] Includes SAEs in footnote b plus the following: IM101332: stomatitis/paraesthesia (PBO); IM101158: anaphylactic reaction, infusion-related reaction (10/10), osteonecrosis (3/3), muscular weakness, drug eruption, and paraesthesia (PBO)

[d] IM101332: *Pneumocystis jirovecii* infection, gastroenteritis, and respiratory tract infection in the abatacept group; IM101158: osteomyelitis (30/10 mg/kg)

[e] IM101332: invasive ductal breast carcinoma and B-cell lymphoma in the PBO group; IM101158: basal cell carcinoma (30/10 mg/kg)

Abbreviations: AEs - adverse events, ALT - alanine aminotransferase, IV - intravenous, NA - not applicable, NE - not evaluated, PBO - placebo, SAEs - serious adverse events,

SC - subcutaneous

Infections

Study IM101158

Infections were the most common AEs reported during the ST period. A similar percentage of subjects in each treatment group had an AE in the SOC Infections and Infestations, up to 56 days after the last infusion in the ST period or the start of the LT period, whichever occurred first (see Table 52). These reported events included bacterial, viral, and fungal infections. Nasopharyngitis was the most frequently reported infection in all 4 treatment groups. All reported infection and infestation AEs during the ST period were mild or moderate in severity, except for 1 event in the abatacept 30/10 mg/kg group (osteomyelitis, very severe).

The one case of osteomyelitis led to discontinuation of the treatment drug. The subject, a 41-year-old female in the abatacept 30/10 mg/kg group, was reported to have osteomyelitis (third digit in the right foot) with an onset on Day 64 (same day as Day 57 infusion). The subject was discontinued as a result of this SAE, which was assessed by the investigator as very severe and possibly related to study drug. The osteomyelitis was ongoing at the time of the data cut-off for the ST period.

No cases of serious infections or infestations were seen in the placebo group.

Table 52 - Infections and Infestations Adverse Events 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)
ACARODERMATITIS	0	0	0	1 (2.4)
PHARYNGITIS STREPTOCOCCAL	0	0	0	1 (2.4)
URINARY TRACT INFECTION	0	0	2 (4.4)	0
PHARYNGITIS	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 RHINITIS	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.

MEDDRA VERSION: 11.1

Source: Annex A, Table S.6.26.

During the LT period, AEs in the SOC Infections and Infestations were reported in 83 subjects (56.5%) in the All Treated Subjects in LT Period population (see Table 53). The most commonly reported infection AEs during the LT period were nasopharyngitis (22.4%), upper respiratory tract infection (10.9%), bronchitis (8.8%), sinusitis (8.2%), and urinary tract infection (6.8%). One AE was assessed as severe in intensity (tooth abscess) and for 5 subjects (3.4%), the reported infection in the LT period was serious (including 2 reports of pneumonia and cellulitis, herpes zoster, pyelonephritis acute and sinusitis each reported once). For 3 of these subjects, the SAEs were assessed as at least possibly related to study treatment (cellulitis, herpes zoster, pyelonephritis acute and pneumonia). None of the SAEs reported during the LT period led to discontinuation of abatacept, but one case of infection (localized infection) did.

Table 53 - Infections and Infestations Adverse Events Reported During the Long-term Period All Treated Subjects in LT 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)

Includes data up to 56 days post the last dose in the long term period.

MEDDRA VERSION: 13.1
Source: Annex B, Table S.6.26A.

Study IM101332

Also in Study IM101332 Infections and infestations were the most commonly reported AEs during the ST period and were reported in 57 (26.8%) subjects and 63 (29.9%) subjects in abatacept and placebo group, respectively (see Table 54). Nasopharyngitis and upper respiratory infections were the most common AEs and were reported slightly more often in the placebo group (4.2% and 2.8% in the abatacept group, 5.2% and 6.6% in the placebo group, respectively). The only SAE of infection that was considered related to study drug was a case of *Pneumocystis jirovecii* infection, which also led to discontinuation of the treatment:

The subject a 59-year old female, who had a medical history of smoking, chronic obstructive pulmonary disease, type II diabetes, and coronary artery disease. The treatment was discontinued after 18 injections of abatacept after the subject was hospitalized for suspected pneumonia and a serious adverse event of Grade 2 *Pneumocystis jirovecii* infection.

Adverse events reported in at least 2% of subjects and in more subjects in the abatacept vs placebo groups included urinary tract infections (4.2% vs 0.9% of subjects), bronchitis (3.3% vs 2.4% of subjects), and gastroenteritis (3.3% vs 2.4% of subjects).

Table 54 - Adverse Events Reported During the Short-term Period: As-treated Population

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept SC (N=213)	Placebo (N=211)
TOTAL SUBJECTS WITH AE	116 (54.5)	112 (53.1)
INFECTIONS AND INFESTATIONS	57 (26.8)	63 (29.9)
NASOPHARYNGITIS	9 (4.2)	11 (5.2)
URINARY TRACT INFECTION	9 (4.2)	2 (0.9)
BRONCHITIS	7 (3.3)	5 (2.4)
GASTROENTERITIS	7 (3.3)	5 (2.4)
UPPER RESPIRATORY TRACT INFECTION	6 (2.8)	14 (6.6)
INFLUENZA	4 (1.9)	3 (1.4)
SINUSITIS	4 (1.9)	3 (1.4)
CONJUNCTIVITIS	3 (1.4)	1 (0.5)
ORAL HERPES	3 (1.4)	2 (0.9)
RESPIRATORY TRACT INFECTION	2 (0.9)	3 (1.4)
VIRAL UPPER RESPIRATORY TRACT INFECTION	2 (0.9)	0
CANDIDA INFECTION	1 (0.5)	0
GASTROENTERITIS VIRAL	1 (0.5)	1 (0.5)
GINGIVITIS	1 (0.5)	0
HERPES ZOSTER	1 (0.5)	1 (0.5)
HORDEOLUM	1 (0.5)	0
LOWER RESPIRATORY TRACT INFECTION	1 (0.5)	0
MOLLUSCUM CONTAGIOSUM	1 (0.5)	1 (0.5)
ORAL FUNGAL INFECTION	1 (0.5)	0
ORBITAL INFECTION	1 (0.5)	0
OTITIS MEDIA	1 (0.5)	0
PNEUMOCYSTIS JIROVECII INFECTION	1 (0.5)	0
RESPIRATORY TRACT INFECTION VIRAL	1 (0.5)	0
RHINITIS	1 (0.5)	0
SUBCUTANEOUS ABSCESS	1 (0.5)	0
TINEA CRURIS	1 (0.5)	2 (0.9)
TONSILLITIS	1 (0.5)	0
TOOTH ABSCESS	1 (0.5)	2 (0.9)
TRACHEITIS	1 (0.5)	0
VULVOVAGINAL CANDIDIASIS	1 (0.5)	0
VULVOVAGINAL MYCOTIC INFECTION	1 (0.5)	0
ACUTE SINUSITIS	0	2 (0.9)
APPENDICITIS	0	1 (0.5)
BRONCHOPNEUMONIA	0	1 (0.5)
CELLULITIS	0	2 (0.9)
CYSTITIS	0	1 (0.5)
EAR INFECTION	0	1 (0.5)
FUNGAL SKIN INFECTION	0	2 (0.9)
GASTRIC INFECTION	0	1 (0.5)
HELICOBACTER GASTRITIS	0	1 (0.5)
HERPES SIMPLEX	0	1 (0.5)
KIDNEY INFECTION	0	1 (0.5)
ONYCHOMYCOSIS	0	1 (0.5)
ORAL CANDIDIASIS	0	1 (0.5)
PHARYNGITIS	0	2 (0.9)
PHARYNGOTONSILLITIS	0	1 (0.5)
RASH PUSTULAR	0	1 (0.5)
TINEA PEDIS	0	1 (0.5)
TOOTH INFECTION	0	2 (0.9)
VIRAEMIA	0	1 (0.5)

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.
MEDDRA VERSION: 18.0

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During The Cumulative Abatacept Period up to Year 1 Infections and Infestations were the predominant AEs and were reported for 162 (40.7%) subjects. The most common infections that were reported in ≥ 5% of subjects included upper respiratory tract infection (7.0%), bronchitis (6.5%), and nasopharyngitis (6.3%). Up to Year 2 infections were reported in 181 subjects (45.5%). Upper respiratory infections were reported in 33 (8.3%) subjects, bronchitis in 31 (7.8%) subjects, nasopharyngitis in 26 (6.5%) subjects, and urinary tract infections in 22 (5.5%) subjects.

Up to Year 2 AEs of infection were reported in 52.5% the treatment was discontinued due to AEs or SAEs of infection in 7 (1.8%) subjects including 3 subjects during the ST period: gastroenteritis, respiratory tract infection and *Pneumocystis jirovecii* infection; during the OL period in one subject due to oropharyngeal candidiasis and in 3 subjects during LTE due to hepatitis A, Epstein-Barr virus infection and intervertebral discitis.

Serious adverse events of infection were reported in 10 (2.5%) subjects: gastroenteritis (2 subjects) and *Pneumocystis jirovecii* infection during the ST period; appendicitis, Epstein-Barr virus infection, pneumonia and pyelonephritis during the OL period; and osteomyelitis, intervertebral discitis and cellulitis during the LTE.

Malignancies

Study IM10158

A single malignancy was reported during the ST period: basal cell carcinoma in a subject in the abatacept 30/10 mg/kg group (see Table 55). This event occurred in a 66-year-old female subject (IM101158-28-152) on Day 124, and was assessed as mild in intensity and possibly related to study drug. The subject completed the ST period and continued in the LT period without dose modification. The basal cell carcinoma was considered a serious AE, and resolved after 165 days during the LT period. During the LT period malignancies were reported in 2 subjects (1.4%) treated with abatacept. 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 and neither malignancy 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 LT period (Day 673) and therefore not included to the summary table. The subject (IM101158-2-100) had a history of exposure to Agent Orange, a known carcinogen, while a soldier in the Vietnam War.

Study IM101332

In placebo group two (2) cases of malignancy were reported; an invasive ductal breast carcinoma and a B-cell lymphoma. No malignancies were reported in the abatacept group during the ST period.

During The Cumulative Abatacept Period malignancies were reported in 4 subjects during the OL period (1.0%) including cases of: prostate cancer, a carcinoma in situ of skin, a squamous cell carcinoma of skin and a transitional cell carcinoma. The subject with squamous cell carcinoma had a medical history of a basal cell carcinoma of the nose. The case of transitional cell carcinoma was considered to be related to abatacept therapy by the investigator, other malignancies were considered unrelated.

Autoimmune Disorders

Study IM101158

Autoimmune disorder AEs (prespecified) were reported during the ST period for a total of 4 subjects, including 3 subjects (7.5%) in the abatacept 10/10 mg/kg group (severe psoriasis, mild psoriasis and moderate psoriatic arthropathy) and 1 subject (2.4%) in the placebo group. Of the 3 cases of autoimmune disorders reported in the abatacept groups none were serious and all were related to the underlying disease.

During the LT period Autoimmune disorders (prespecified) AEs of psoriasis were reported for 5 (3.4%) subjects. For one subject the AE was assessed as serious. All 5 cases were assessed as unlikely or not related to study treatment and related to the underlying disease, and the treatment was continued.

Study IM101332

No autoimmune events were reported in either treatment group during the ST period. Of note, unlike in study IM101158, the investigators were requested not to report AEs of psoriatic arthritis or psoriasis

unless the event represented a new form of psoriasis or was an SAE. During the ST Period Adverse Events of New Psoriasis or SAEs of Psoriasis or Psoriatic Arthropathy (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). No cases of an AE or SAE of psoriasis were reported in abatacept-treated subjects.

During The Cumulative Abatacept Period prespecified autoimmune events were reported in 3/398 subjects: a case of uveitis was reported in 1 subject during the OL Period and coeliac disease and a case of hyperthyroidism each in one subject during the LT extension. None of these events was considered related to abatacept or led to discontinuation of the treatment.

Worsening or New Psoriasis or Psoriatic Arthropathy

Six (6) subjects had AEs or SAEs of psoriasis during the OL Period. The cases included: SAEs of psoriatic arthropathy in 2 subjects, an AE of psoriasis, an SAE of psoriasis, an AE of skin plaque and a SAE of erythrodermic psoriasis. The two subjects with psoriatic arthopathy continued the treatment, but the four (4) subjects with AEs or SAEs of psoriasis discontinued abatacept therapy due to a lack of efficacy. During the LTE SAEs of psoriatic arthropathy were reported in 2 subjects. These events did not lead to discontinuation of the treatment.

The subject originally randomized to abatacept treatment, was reported with an AE and also an SAE of erythrodermic psoriasis during the Open-label Period. During the treatment with abatacept, the investigator had noted gradual worsening of psoriasis eventually necessitating the use of topical steroids and intramuscular dexamethasone before the subject was discontinued from the treatment due to lack of efficacy. A week after (Day 310) the subject had received the last dose of abatacept, the subject was noted to have lesions that were confluent. Her PASI score was 53.8. She also experienced significant itching, pain, and chills. On Day 331, in subject's first follow up visit, upon examination 90% of the subject's body surface was affected by psoriasis. The subject was hospitalized due to serious adverse event of Grade 2 erythrodermic psoriasis on the same day. The subject received treatment with cyclosporine. At the time of database lock, the event of erythrodermic psoriasis and treatment with cyclosporine were ongoing. The investigator considered the event of erythrodermic psoriasis to be related to the study therapy.

Infusional Adverse Events (Prespecified) - Study IM101158

Acute infusional AEs are a subset of peri-infusional events occurring within 24 hours after the start of study drug infusion, and therefore, the percentages are not additive. Acute infusional AEs (prespecified), occurring within 1 hour of infusion, were reported during the ST 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 and 0 in the placebo group. These AEs included blood pressure increased (2 events), dizziness, dyspnoea and flushing in 30/10 group and infusion related reaction, anaphylactic reaction and dizziness in 10/10 group. One AE was severe (non-serious): a 26 year-old female (subject IM101158-83-173), in the abatacept 10/10 mg/kg group, experienced a severe anaphylactic reaction within 1 hour of the onset of the second infusion of abatacept on Day 15. The subject was discontinued from the study.

During the ST period, 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 experienced a peri-infusional AE (prespecified). The majority of AEs were of mild to moderate severity and 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), BP increased (n = 2), and dizziness (n = 2).

During the LT period acute infusional AEs (prespecified) were reported by 4 (2.7%) treated subjects. These cases included 2 reports of infusion-related reaction, and single reports each of pruritus and flushing. Peri-infusional AEs, reported within 24 hours after the start of study drug infusion, were reported by 11 (7.5%) subjects during the LT period. One case of headache was assessed as severe; all other cases were mild to moderate in intensity. No peri-infusional AE during the LT period led to discontinuation of the study drug.

Adverse Events within 24 Hours of Study Drug Administration - Study IM101332

During the ST Period 39 (18.3%) subjects in the abatacept group and 39 (18.5%) subjects in the placebo group reported AEs within 24 h of drug administration. The most frequently reported AEs within 24 hours were in the SOC of Infections and Infestations: 13 subjects (6.1%, IR: 15.1/100 p-y) in the abatacept group and 15 subjects (6.2%; IR: 18.5/100 p-y) in the placebo group. None of these AEs were suggestive of systemic drug reactions.

During the Cumulative abatacept period up to Year 1 94 (23.6%) subjects had an AE within 24 hours of abatacept administration. The most frequently reported AEs within 24 hours (≥ 1.0%) were infections and included nasopharyngitis (1.3%), urinary tract infection (1.3%), and bronchitis (1.0%). 2 AEs were severe in intensity: an AE of renal colic during the double-blind period, and an AE of abdominal pain upper during the OL Period. AEs leading to discontinuation were abdominal pain upper and uterine leiomyoma.

Up to Year 2, 131 (32.9%) subjects had an AE within 24 hours of abatacept administration. Most frequently (≥ 1.0%) reported AEs included nasopharyngitis (1.5%), urinary tract infection (1.3%), back pain (1.3%), and bronchitis (1.3%), dyslipidemia (1.0%), upper respiratory infection (1.0%), and depression (1.0%). Four subjects had AEs within 24 hours during the LTE that were serious; these SAEs included dermoid cyst, accidental overdose, abdominal pain upper, and psoriatic arthropathy.

Local Injection Site Reactions (Pre-specified) - Study IM101332

Pre-specified local injection site reactions (IR: 1.23/100 p-y), all mild in intensity, were reported in 5/398 subjects during the cumulative abatacept period up to Year 2: 1 subject with an injection site reaction (related to abatacept), 1 subject with 2 episodes of puncture site erythema (both episodes not related to abatacept), 1 subject with 3 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 2 episodes of pruritus (related to abatacept). Therapy was not discontinued due to these AEs in any of the subjects.

Serious adverse event/deaths/other significant events

No deaths were reported in Study IM101158. Up to year 2 in Study IM101332, no deaths have been reported.

Study IM101158

During the double-blind period a total of 4 (9.3%), 2 (5%), 0 and 1 (2%) subjects reported SAEs in abatacept 30/10 mg/kg, abatacept 10/10 mg/kg, abatacept 3/3 mg/kg and placebo groups, respectively (see Table 55). SAEs (6) reported in abatacept-treated subjects were: Cholecystitis acute (SOC Hepatobiliary disorders), osteomyelitis and gastroenteritis (SOC Infections and infestations), overdose (SOC Injury, poisoning and procedural complications), basal cell carcinoma (SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) and dizziness (SOC Nervous system disorders). Each SAE was reported for one subject. In placebo-group one subject was reported with Personality disorder and psychiatric decompensation (SOC Psychiatric disorders).

Table 55 - Serious Adverse Events 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 SERIOUS ADVERSE EVENTS, n (%)	4 (9.3)	2 (5.0)	0	1 (2.4)
HEPATOBILIARY DISORDERS	1 (2.3)	0	0	0
CHOLECYSTITIS ACUTE	1 (2.3)	0	0	0
INFECTIONS AND INFESTATIONS	1 (2.3)	1 (2.5)	0	0
OSTEOMYELITIS	1 (2.3)	0	0	0
GASTROENTERITIS	0	1 (2.5)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (2.3)	0	0	0
OVERDOSE	1 (2.3)	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (2.3)	0	0	0
BASAL CELL CARCINOMA	1 (2.3)	0	0	0
NERVOUS SYSTEM DISORDERS	0	1 (2.5)	0	0
DIZZINESS	0	1 (2.5)	0	0
PSYCHIATRIC DISORDERS	0	0	0	1 (2.4)
PERSONALITY DISORDER	0	0	0	1 (2.4)
PSYCHIATRIC DECOMPENSATION	0	0	0	1 (2.4)

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.

MEDDRA VERSION: 11.1
PROGRAM SOURCE: /wwbdm/clin/proj/im/101/158/val/cpp/csrst/programs/rt-ae-sae-db-v01.sas 27APR09 14:01

SAEs were reported for a total of 20 (13.6%) and 24 (14.9%) subjects in All Treated Subjects in LT Period population and in All Abatacept-Treated Subjects in ST+LT Periods, respectively. 4 SAEs were considered related by the investigator during the LT period and 5 in ST + LT Periods. One subject discontinued due to an SAE.

Of the total 24 subjects (14.9%) (see Table 56) with SAEs in SOC Musculoskeletal and connective tissue disorders were reported in 8 (5.0%) subjects including osteoarthritis in 4 subjects (2.5%), arthritis in 2 subjects (1.2%) and groin pain, intervertebral disc protrusion and psoriatic arthropathy in 1 subject each (0.6%). In SOC Infections and infestations SAEs were reported in 6 subjects (3.7%), including gastroenteritis in 2 subjects (1.2%), pneumonia in 2 subjects (1.2%) and cellulitis, herpes zoster, osteomyelitis, pyelonephritis acute and sinusitis in 1 subject (0.6%) each. SAEs in SOC Cardiac disorders were reported in 4 subjects (2.5 %), including atrial fibrillation in 2 subjects (1.2%) and acute coronary syndrome, aortic valve incompetence and cardiac failure each in 1 subject (0.6%).

The SAE of cardiac failure in Subject IM101158-28-122 (ST cohort: abatacept 10/10 mg/kg) was assessed as possibly related to treatment. The subject was a 69-year-old female with no reported medical history of cardiac disease. Relevant past medications include metoprolol. She developed cardiac failure on Day 323, 21 days after the Day 309 scheduled infusion of abatacept in the LT period. The subject was treated with furosemide and acetylsalicyclic acid, and the event was considered resolved after 4 days. The cardiac failure was assessed by the investigator as moderate in intensity and possibly related to study drug. The subject remained in the study and was subsequently discontinued on Day 812 due to administrative reasons by the sponsor (i.e., study termination).

In SOC Injury, poisoning and procedural complications 3 SAEs were reported in a total of 3 subjects (1.9%) including humerus fracture, overdose and tendon rupture in 1 subject each (0.6%). In SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps) 3 SAEs were reported in two subjects: basal cell carcinoma, Bowen´s disease, lentigo maligna stage unspecified. SAEs in SOC Nervous system disorders were reported in 2 subjects (1.2%), including dizziness and migraine for one subject (0.6%) each. In SOC Respiratory, thoracic and mediastinal disorders, SAEs were reported in 2 subjects (1.2%), including apnoe and asthma for 1 subject (0.6%) each. Additionally in SOC Gastrointestinal disorders, gastritis was reported for one subject (0.6%); in SOC Hepatobiliary disorders, cholecystitis

acute for 1 subject (0.6%); in SOC Immune system disorders, anaphylactic reaction for 1 subject (0.6%). Additionally in SOC Metabolism and nutrition disorders, dehydration was reported for 1 subject (0.6%); in SOC Psychiatric disorders, personality disorder for one subject (0.6%), in SOC renal and urinary disorders, urinary retention for one subject (0.6%), in SOC Skin and subcutaneous tissue disorders, psoriasis for one subject (0.6%) and in SOC Social circumstances, family stress for one subject (0.6%).

The SAEs that belong categories of AEs of special interest (infections, malignancies, autoimmune disorders and infusion reactions) are discussed separately under section *Adverse events*.

Table 56 - Serious Adverse Events Reported During the Short Term and Long Term Period: All Abatacept-treated Analysis Population

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	All Abatacept N = 161
TOTAL SUBJECTS WITH SAE	24 (14.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (5.0)
OSTEOARTHRITIS	4 (2.5)
ARTHRITIS	2 (1.2)
GROIN PAIN	1 (0.6)
INTERVERTEBRAL DISC PROTRUSION	1 (0.6)
PSORIATIC ARTHROPATHY	1 (0.6)
INFECTIONS AND INFESTATIONS	6 (3.7)
GASTROENTERITIS	2 (1.2)
PNEUMONIA	2 (1.2)
CELLULITIS	1 (0.6)
HERPES ZOSTER	1 (0.6)
OSTEOMYELITIS	1 (0.6)
PYELONEPHRITIS ACUTE	1 (0.6)
SINUSITIS	1 (0.6)
CARDIAC DISORDERS	4 (2.5)
ATRIAL FIBRILLATION	2 (1.2)
ACUTE CORONARY SYNDROME	1 (0.6)
AORTIC VALVE INCOMPETENCE	1 (0.6)
CARDIAC FAILURE	1 (0.6)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (1.9)
HUMERUS FRACTURE	1 (0.6)
OVERDOSE	1 (0.6)
TENDON RUPTURE	1 (0.6)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (1.2)
BASAL CELL CARCINOMA	1 (0.6)
BOWEN'S DISEASE	1 (0.6)
LENTIGO MALIGNA STAGE UNSPECIFIED	1 (0.6)
NERVOUS SYSTEM DISORDERS	2 (1.2)
DIZZINESS	1 (0.6)
MIGRAINE	1 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (1.2)
APNOEA	1 (0.6)
ASTHMA	1 (0.6)
GASTROINTESTINAL DISORDERS	1 (0.6)
GASTRITIS	1 (0.6)
HEPATOBILIARY DISORDERS	1 (0.6)
CHOLECYSTITIS ACUTE	1 (0.6)
IMMUNE SYSTEM DISORDERS	1 (0.6)
ANAPHYLACTIC REACTION	1 (0.6)
METABOLISM AND NUTRITION DISORDERS	1 (0.6)
DEHYDRATION	1 (0.6)

PSYCHIATRIC DISORDERS	1	(0.6)
PERSONALITY DISORDER	1	(0.6)
RENAL AND URINARY DISORDERS	1	(0.6)
URINARY RETENTION	1	(0.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	(0.6)
PSORIASIS	1	(0.6)
SOCIAL CIRCUMSTANCES	1	(0.6)
FAMILY STRESS	1	(0.6)

Includes data up to 56 days post the last Abatacept Infusion.

MEDDRA VERSION: 13.1
PROGRAM SOURCE: /wwbdm/clin/proj/im/101/158/val/cpp/csrlt/programs/rt-ae-saeaba-v01.sas

Study IM101332

SAEs were reported in 6 (2.8%) subjects in the abatacept group and 9 (4.3%) subjects in the placebo group during the ST period (see Table 57). SAEs considered treatment-related were reported in 1 (0.5%) subject in each group: *Pneumocystis jirovecii* infection in the abatacept group and increased ALT in the placebo group. Both subjects discontinued the treatment. Discontinuation of treatment due to AEs was reported in 1.4% and 1.9% of subjects in the abatacept and placebo groups, respectively. Overall, 3 subjects in each treatment group discontinued study drug due to SAEs.

Three (3) subjects (1.4%) in the abatacept group and 2 subjects (0.9%) in the placebo group experienced SAEs of infection: in the abatacept group, 2 subjects had gastroenteritis and 1 subject had a *Pneumocystis jirovecii* infection; in the placebo group, 1 subject had appendicitis and 1 subject had cellulitis. Two (2) malignancies (0.9%) were reported, both in the placebo group (B-cell lymphoma and invasive ductal breast carcinoma). Other serious AEs reported for abatacept-treated subjects included each reported in 1 (one) subject: interstitial lung disease and pulmonary embolism (SOC Respiratory, thoracic and mediastinal disorders), intervertebral disc protrusion (SOC Musculoskeletal and connective tissue disorders) and venous thrombosis (SOC Vascular disorders). In placebo-group SAEs were also reported for 1 subject each: acute chest syndrome (SOC Respiratory, thoracic and mediastinal disorders), psoriatic arthropathy (SOC Musculoskeletal and connective tissue disorders), peripheral artery thrombosis (SOC Vascular disorders), febrile neutropenia (SOC Blood and lymphatic system disorders), cholecystitis acute (SOC Hepatobiliary disorders), anaphylactic reaction (SOC Immune system disorders), vascular pseudoaneurysm (SOC Injury, poisoning and procedural complications) and alanine aminotransferase increased (SOC Investigations).

AEs of special interest (infections, malignancies, autoimmune events, local injection site reactions and AEs within 24 hours of administrations are further discussed separately by category under section *Adverse events*.

Table 57 - Serious Adverse Events Reported During the Short-term Period – As-treated Population

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept SC (N=213)	Placebo (N=211)
TOTAL SUBJECTS WITH AE	6 (2.8)	9 (4.3)
INFECTIONS AND INFESTATIONS	3 (1.4)	2 (0.9)
GASTROENTERITIS	2 (0.9)	0
PNEUMOCYSTIS JIROVECII INFECTION	1 (0.5)	0
APPENDICITIS	0	1 (0.5)
CELLULITIS	0	1 (0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.9)	1 (0.5)
INTERSTITIAL LUNG DISEASE	1 (0.5)	0
PULMONARY EMBOLISM	1 (0.5)	0
ACUTE CHEST SYNDROME	0	1 (0.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.5)	1 (0.5)
INTERVERTEBRAL DISC PROTRUSION	1 (0.5)	0
PSORIATIC ARTHROPATHY	0	1 (0.5)
VASCULAR DISORDERS	1 (0.5)	1 (0.5)
VENOUS THROMBOSIS	1 (0.5)	0
PERIPHERAL ARTERY THROMBOSIS	0	1 (0.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (0.5)
FEBRILE NEUTROPENIA	0	1 (0.5)
HEPATOBILIARY DISORDERS	0	1 (0.5)
CHOLECYSTITIS ACUTE	0	1 (0.5)
IMMUNE SYSTEM DISORDERS	0	1 (.5)
ANAPHYLACTIC REACTION	0	1 (0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.5)
VASCULAR PSEUDOANEURYSM	0	1 (0.5)
INVESTIGATIONS	0	1 (0.5)
ALANINE AMINOTRANSFERASE INCREASED	0	1 (0.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	2 (0.9)
B-CELL LYMPHOMA	0	1 (0.5)
INVASIVE DUCTAL BREAST CARCINOMA	0	1 (0.5)

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
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In the Cumulative Abatacept population up Year 1, a total of 34 subjects had SAEs (8.5%), of which 5 (1.3%) were considered related and 8 (2.0%) led to discontinuation of abatacept. The most common types of SAEs were infections (in SOC Infections and infestations) in 7 subjects (1.8%). During the OL period 4 subjects (1.3%) had SAEs that were assessed as related: pyelonephritis, dyspnea, erythrodermic psoriasis, and transitional cell carcinoma reported in 1 subject each. 5 subjects discontinued during the OL Period due to SAEs: a transitional cell carcinoma, prostate cancer, colitis, biliary dilatation, and uterine leiomyoma.

Up to Year 2, SAEs were reported in 49 (12.3%) abatacept-treated subjects. The most common types of SAEs were in SOC Musculoskeletal and connective tissue disorders in 12 subjects (3.0%) and infections and infestations in 10 subjects (2.5%) (see Table 58). 10 subjects (2.5%) had SAEs that were considered related by the investigator. During the LTE period, the treatment-related SAEs included: osteomyelitis, intervertebral discitis, gastric mucosa erythema, accidental overdose, and cellulitis (all reported in 1 subject each). Up to year 2 SAEs led to discontinuation of abatacept therapy in 9 (2.3%) subjects including an SAE of intervertebral discitis reported in 1 subject during the LTE period.

Table 58 - Incidence Rates of Serious Adverse Events 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)

SYSTEM ORGAN CLASS (SOC) PREFERRED TERM (PT)	ABATACEPT SC EXPOSURE: SUBJECTS WITH EVENT (%)	EXPOSURE (PERSON-YEARS)	RATE: (INCIDENCE/100 PERSON-YEARS)	POISSON 95% CI
TOTAL SUBJECTS WITH AE	49 (12.3)	525.03	9.33	(7.05, 12.35)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	12 (3.0)	547.54	2.19	(1.24, 3.86)
OSTEOARTHRITIS	4 (1.0)	552.48	0.72	(0.27, 1.93)
PSORIATIC ARTHROPATHY	3 (0.8)	553.36	0.54	(0.17, 1.68)
OSTEONECROSIS	2 (0.5)	554.26	0.36	(0.09, 1.44)
ROTATOR CUFF SYNDROME	2 (0.5)	552.20	0.36	(0.09, 1.45)
CHONDROPATHY	1 (0.3)	553.86	0.18	(0.03, 1.28)
INTERVERTEBRAL DISC PROTRUSION	1 (0.3)	553.84	0.18	(0.03, 1.28)
METATARSALGIA	1 (0.3)	554.47	0.18	(0.03, 1.28)
INFECTIONS AND INFESTATIONS	10 (2.5)	548.11	1.82	(0.98, 3.39)
GASTROENTERITIS	2 (0.5)	553.02	0.36	(0.09, 1.45)
APPENDICITIS	1 (0.3)	553.41	0.18	(0.03, 1.28)
CELLULITIS	1 (0.3)	554.28	0.18	(0.03, 1.28)
EPSTEIN-BARR VIRUS INFECTION	1 (0.3)	553.19	0.18	(0.03, 1.28)
INTERVERTEBRAL DISCITIS	1 (0.3)	554.56	0.18	(0.03, 1.28)
OSTEOMYELITIS	1 (0.3)	554.19	0.18	(0.03, 1.28)
PNEUMOCYSTIS JIROVECII INFECTION	1 (0.3)	554.56	0.18	(0.03, 1.28)
PNEUMONIA	1 (0.3)	554.62	0.18	(0.03, 1.28)
PYELONEPHRITIS	1 (0.3)	553.94	0.18	(0.03, 1.28)
GASTROINTESTINAL DISORDERS	7 (1.8)	551.70	1.27	(0.60, 2.66)
ABDOMINAL PAIN UPPER	1 (0.3)	554.40	0.18	(0.03, 1.28)
COLITIS	1 (0.3)	554.57	0.18	(0.03, 1.28)
DIARRHOEA	1 (0.3)	553.78	0.18	(0.03, 1.28)
GASTRIC MUCOSA ERYTHEMA	1 (0.3)	553.80	0.18	(0.03, 1.28)
INGUINAL HERNIA	1 (0.3)	554.15	0.18	(0.03, 1.28)
PANCREATITIS	1 (0.3)	554.65	0.18	(0.03, 1.28)
UPPER GASTROINTESTINAL HAEMORRHAGE	1 (0.3)	554.60	0.18	(0.03, 1.28)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	5 (1.3)	553.14	0.90	(0.38, 2.17)
CARCINOMA IN SITU OF SKIN	1 (0.3)	554.25	0.18	(0.03, 1.28)
PARATHYROID TUMOUR BENIGN	1 (0.3)	554.23	0.18	(0.03, 1.28)
PROSTATE CANCER	1 (0.3)	554.53	0.18	(0.03, 1.28)
TRANSITIONAL CELL CARCINOMA	1 (0.3)	554.41	0.18	(0.03, 1.28)
UTERINE LEIOMYOMA	1 (0.3)	554.55	0.18	(0.03, 1.28)
CARDIAC DISORDERS	3 (0.8)	552.22	0.54	(0.18, 1.68)
ACUTE CORONARY SYNDROME	1 (0.3)	553.52	0.18	(0.03, 1.28)
CORONARY ARTERY DISEASE	1 (0.3)	553.52	0.18	(0.03, 1.28)
MYOCARDIAL ISCHAEMIA	1 (0.3)	554.60	0.18	(0.03, 1.28)
HEPATOBILIARY DISORDERS	3 (0.8)	552.97	0.54	(0.17, 1.68)
CHOLECYSTITIS ACUTE	2 (0.5)	553.19	0.36	(0.09, 1.45)
BILIARY DILATATION	1 (0.3)	554.49	0.18	(0.03, 1.28)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.8)	553.40	0.54	(0.17, 1.68)
DYSPNOEA	1 (0.3)	554.61	0.18	(0.03, 1.28)
INTERSTITIAL LUNG DISEASE	1 (0.3)	554.63	0.18	(0.03, 1.28)
PULMONARY EMBOLISM	1 (0.3)	553.58	0.18	(0.03, 1.28)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.5)	553.06	0.36	(0.09, 1.45)
CHEST PAIN	1 (0.3)	554.40	0.18	(0.03, 1.28)
INCARCERATED HERNIA	1 (0.3)	553.37	0.18	(0.03, 1.28)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.5)	554.06	0.36	(0.09, 1.44)
ACCIDENTAL OVERDOSE	1 (0.3)	554.52	0.18	(0.03, 1.28)
FALL	1 (0.3)	554.25	0.18	(0.03, 1.28)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.5)	554.25	0.36	(0.09, 1.44)
ERYTHRODERMIC PSORIASIS	1 (0.3)	554.63	0.18	(0.03, 1.28)
PSORIASIS	1 (0.3)	554.32	0.18	(0.03, 1.28)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.3)	553.88	0.18	(0.03, 1.28)
DERMOID CYST	1 (0.3)	553.88	0.18	(0.03, 1.28)
EAR AND LABYRINTH DISORDERS	1 (0.3)	553.16	0.18	(0.03, 1.28)
MENIERE'S DISEASE	1 (0.3)	553.16	0.18	(0.03, 1.28)
METABOLISM AND NUTRITION DISORDERS	1 (0.3)	554.17	0.18	(0.03, 1.28)
OBESITY	1 (0.3)	554.17	0.18	(0.03, 1.28)
NERVOUS SYSTEM DISORDERS	1 (0.3)	553.75	0.18	(0.03, 1.28)
TRANSIENT ISCHAEMIC ATTACK	1 (0.3)	553.75	0.18	(0.03, 1.28)
RENAL AND URINARY DISORDERS	1 (0.3)	553.33	0.18	(0.03, 1.28)
NEPHROLITHIASIS	1 (0.3)	553.33	0.18	(0.03, 1.28)
VASCULAR DISORDERS	1 (0.3)	553.79	0.18	(0.03, 1.28)
VENOUS THROMBOSIS	1 (0.3)	553.79	0.18	(0.03, 1.28)

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: 18.1

Program Source: s:\rho\kms\orencia\studies\iml01-332\tables\rt-ae-incsaecumyr2.sas 24MAR2016 12:19

SAEs of special interest (infections, malignancies, autoimmune events, local injection site reactions and AEs within 24 hours of administrations) are additionally discussed under each category in section *Adverse events*.

Laboratory findings

Study IM101158

During the ST period, the following MAs occurred at ≤ 5% of subjects: low lymphocyte counts: 4.7%, 0%, and 13.3% in the abatacept 30/10, 10/10, and 3/3 mg/kg groups, respectively, and 2.4% in the placebo group; low serum glucose: 0%, 5.0%, and 8.9% in the abatacept 30/10, 10/10, and 3/3 mg/kg groups, respectively, and 0% in the placebo group; high serum glucose: 2.3%, 5.0%, and 8.9% in the abatacept.

The most frequently occurring MA abnormality was markedly low lymphocytes. Lymphopenia was not reported as an AE in any subject during the ST period. One subject in the abatacept 30/10 mg/kg group had a marked elevation in ALT during the ST period. The elevated value was reported an AE with severe intensity and unlikely related to the study drug. At the final assessment the value had decreased from 186 U/L to 88 U/L. The baseline value was 41 U/L. Levels of all clinical laboratory parameters generally remained stable in both treatment groups during the ST period, however mean reductions from baseline at Day 169 in serum IgA, IgG, and IgM were noted in the 3 abatacept groups, but similar reductions were not observed in the placebo group.

Across all groups 25 subjects had positive ANA status and 15 subjects had positive anti-dsDNA at baseline. One subject from placebo group converted from negative anti-dsDNA status at baseline to a positive status at Day 169, for others the status remained unchanged.

The most common abnormalities seen during the LT period were leukocytosis in seven subjects (4.8%) and markedly low lymphocytes in 6 subjects (4.1%). Markedly elevated ALT and AST values were reported during the LT period in 2 subjects (1 subject each, 0.7%). MAs occurring at ≥5% were high eosinophils in 8.2% of subjects and high serum glucose in 7.6% of subjects. Of the 16 subjects with MAs of high serum glucose in the ST and/or LT periods, 9 (56.3%) had a medical history that included diabetes mellitus.

In 4 subjects with leukocytosis, the baseline leukocyte value was high and for 4 subjects the markedly elevated leukocyte value was an isolated finding. Leukocytosis was reported as an AE in 1 subject, and was assessed as moderate in severity and unlikely related to study drug. The maximum leukocytes value in this subject was 21.70 x 103/µL (baseline, 11.20 x 103/µL), and the values remained elevated after the subject withdrew from the study due to lack of efficacy on Day 312 (final value on Day 340 was 14.60 x 103/µL). This subject was also reported to have a humerus fracture and fungal skin infection at the time of the marked laboratory abnormality. Lymphopenia was reported as an AE in 1 subject and was assessed as mild and unlikely related to study drug; no marked laboratory abnormality was reported in this subject.

Study IM101332

During the ST period markedly abnormal laboratory values were uncommon in both treatment groups and were reported in a similar proportion of subjects in each group. No clinically relevant trends were observed in either treatment group. 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. Regarding kidney function tests, marked elevations were noted in < 2% of subjects in the abatacept group and < 1% of subjects in the placebo group. 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 (245 U/L) that was considered related to study drug by the investigator and resulted in discontinuation of the treatment.

During The Cumulative Abatacept Period up to Year 1, 7 subjects (1.8%) had elevations in AST and 10 subjects (1.8%) in ALT that met the marked laboratory criteria. Two subjects had treatment-related AEs of increased transaminases which led to discontinuation of abatacept during the OL Period. 20 (5.1%) subjects had elevations in serum glucose and 18 (5.8%) of subjects with elevations in fasting triglycerides that met the MA criteria. 14/20 (70.0%) had had a medical history that included diabetes mellitus. No subjects discontinued study therapy due to elevations in fasting triglycerides or glucose. Lymphopenia is noted in 11 subjects (2.8%) and leucocytosis in 10 subjects (2.5%)

Up to Year 2, lymphopenia was noted in 15 subjects (3.8%), leucocytosis in 13 subjects (13.3%), elevated AST in 9 subjects (2.3%) and ALT in 13 subjects (3.3%), elevations in serum glucose in 27 subjects (6.8%) and elevations in fasting triglycerides in 18 subjects (5.7%).

Additionally during The Cumulative Abatacept Period in more than 2 % of the subjects elevated levels of eosinophils, GGT, BUN, creatinine and low levels of phosphorus were noted.

Safety in special populations

Study IM101158

No subgroup analyses of safety were performed in IM101158.

Study IM101332

Subgroup analyses by age (< 65 years old, >65 years old, baseline weight (60-100 kg, > 100 kg), gender (male, female), geographic region (North America, Europe, South America, ROW), MTX use at Day 1 (yes, no), TNFi-exposed (yes, no), steroid use (yes, no)) were performed on data from the ST period of IM101332. The safety profile of abatacept was generally similar in subgroups. Urinary tract infections were reported more frequently in females than males treated with abatacept, but in general, individual AEs were reported by similar proportions of female and male subjects.

Table 59 - Adverse Events (PTs) Reported in at least 5 % of Subjects During the Short-term Period by Concomitant Methotrexate Use, Prior Exposure to TNFi Agents, and Concomitant Oral Steroid Use –As-treated Population

	MTX Use at Day 1 Yes		MTX Use at Day 1: No	
SYSTEM ORGAN CLASS (SOC) (%) 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)
INFECTIONS AND INFESTATIONS	35 (27.1)	43 (33.9)	22 (26.2)	20 (23.8)
UPPER RESPIRATORY TRACT INFECTION	3 (2.3)	10 (7.9)	3 (3.6)	4 (4.8)
NASOPHARYNGITIS	7 (5.4)	7 (5.5)	2 (2.4)	4 (4.8)
GASTROENTERITIS	2 (1.6)	5 (3.9)	5 (6.0)	0
URINARY TRACT INFECTION	4 (3.1)	2 (1.6)	5 (6.0)	0
	TNFi Exposed: Yes		**TNFi Exposed: No**	
SYSTEM ORGAN CLASS (SOC) (%) 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)
INFECTIONS AND INFESTATIONS	32 (24.8)	36 (27.7)	25 (29.8)	27 (33.3)
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)
BRONCHITIS	1 (0.8)	3 (2.3)	6 (7.1)	2 (2.5)
	Oral Steroid Use at Day 1: Yes		**Oral Steroid Use at Day 1: No**	
SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept SC (N=54)	Placebo (N=48)	Abatacept SC (N=159)	Placebo (N=163)
TOTAL SUBJECTS WITH AE	31 (57.4)	24 (50.0)	85 (53.5)	88 (54.0)
INFECTIONS AND INFESTATIONS	15 (27.8)	14 (29.2)	42 (26.4)	49 (30.1)
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)
URINARY TRACT INFECTION	1 (1.9)	1 (2.1)	8 (5.0)	1 (0.6)

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

Source: Table S.6.42 in IM101332 CSR

As safety of abatacept was analysed during The Cumulative Abatacept Period up to Year 2 in subgroups by concomitant MTX and prior TNFi use, no clinically relevant differences were observed in SAEs, AEs, AEs reported in ≥5% of subjects and in AEs of special interest between treatment groups (MTX use yes/no and Prior TNFi use yes/no).

Safety related to drug-drug interactions and other interactions

No new data has been submitted in this application, which was considered acceptable by the CHMP. According to the current approved product information for abatacept the use of abatacept with TNF antagonists or other biologic RA therapy is not recommended due to an increased risk of infections.

Discontinuation due to adverse events

Study IM101158

Adverse events lead to discontinuation of the study drug during the ST period for 7 subjects. Discontinuation of study drug were reported in 1 (2.3%), 2 (5.0%), and 1 (2.2%) subjects in the abatacept 30/10, 10/10, and 3/3 mg/kg groups, respectively, and in 3 (7.1%) subjects in the placebo group during the ST period. Treatment-related AEs leading to discontinuation included osteomyelitis (SAE, abatacept 30/10 mg/kg), anaphylactic reaction (AE, abatacept 10/10 mg/kg), infusion-related reaction (AE, abatacept 10/10 mg/kg), drug eruption (AE, placebo), and paresthesia (AE, placebo).

During the LT period, treatment with abatacept was discontinued in 4 subjects (2.7%) due to an AE. The AEs leading to discontinuation during the LT period were periodontal disease, localized infection, weight decreased, and swelling face. Periodontal disease was assessed as possibly related to study drug.

Study IM101332

During the ST period 1.4 % and 1.9% in the abatacept and the placebo groups, respectively, discontinued study drug due to AEs. In placebo group discontinuation was due to AEs of paresthesia and stomatitis and a SAE of ALT increased. In abatacept treated group 3 subjects discontinued due to SAEs: a *Pneumocystis jirovecii* infection, gastroenteritis and interstitial lung disease. AEs of infection led to discontinuation only in the abatacept group. In The Cumulative Abatacept Period, treatment was discontinued due to AEs in 10 subjects during the OL period and in 4 subjects during the LTE.

Treatment-related AEs which led to discontinuation were *Pneumocystis jirovecii* infection during the ST period, increased transaminases (2 subjects), pruritus and transitional cell carcinoma during OL period and intervertebral discitis during the LTE. SAEs led to discontinuation of abatacept therapy in 8/398 (2.0%) subjects, including the 3 subjects during the ST period and 5 subjects during the OL Period (1 subject each): transitional cell carcinoma, prostate cancer, colitis, biliary dilatation, and uterine leiomyoma).

Immunogenicity (Immunological events)

Immunogenicity directed against biological medicinal product can result in alterations in PK, efficacy, and/or safety profiles. Antibody-mediated clearance of a biologic therapy may reduce drug concentrations, or the antibody response may prevent the drug from binding to its pharmacologic target, both of which can lead to decreased efficacy. Antibody responses can also cause general immune-mediated toxicities, such as systemic infusion reactions, local injection reactions, and hypersensitivity reactions. For abatacept specifically, there is also a theoretical concern that antibodies directed to the CTLA4 portion of abatacept could react with endogenous CTLA4 expressed on T-lymphocytes and potentially cause immunostimulatory effects, leading to worsening of the autoimmune disease abatacept was intended to treat or development of other autoimmune disease/ events.

Study IM101158

Few patients developed anti-abatacept antibodies in the ST period. The immunogenicity rates in PsA of 1/43 (2.3%), 0/40 (0), and 2/45 (4.4%) subjects in the IV abatacept 30/10 mg/kg, 10/10 mg/kg, and 3/3 mg/kg groups, respectively were comparable to the historic immunogenicity rates seen in the RA studies with IV abatacept. One subject had neutralizing antibody activity at 56, but not 85, days post last dose. None of the 3 subjects with anti-abatacept antibodies were reported to have SAEs, acute infusional AEs (prespecified), or autoimmune disorders (prespecified) during the ST period. There was no indication of any adverse impact on efficacy in any of the 3 subjects.

Immunogenicity rates were low in the LT period (Table 60), antibody titres were generally low, and the majority were not persistent. The overall abatacept-induced immunogenicity rate for the LT period ranged from 4.7% (2/43) to 5.4% (2/37), with an on-treatment immunogenicity rate ranging from 0 (0/42) to 5.9% (2/34) and a post-treatment immunogenicity rate of 3.1% (1/32) and 8.0% (2/25). All of the abatacept-induced seropositive responses in the LT period consisted of ‘CTLA4 and possibly Ig´ titers ≥ 10. One subject had neutralizing antibody activity at 56, but not 85, days post last dose. Immunogenicity was persistent for 1 subject with a positive on-treatment result. Medical review of the safety data among subjects with an abatacept-induced seropositive response in the LT period indicated that AEs were not consistent with immunemediated toxicities. Immunogenicity status did not appear to affect efficacy responses.

Table 60 - Proportion of Subjects with Positive Abatacept-induced Responses (ECL Method) Over Time in the Long-term Period: Immunogenicity Population of LT 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.
Treatment groups represent treatment received in the double-blind period.

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Study IM101332

During treatment in the ST period, there were 8/203 subjects (3.9%) in the abatacept group and 17/198 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 (see Table 61) Of the 25 subjects positive for ADAs, 5 subjects in the abatacept group and 13 subjects in the placebo group were Early Escape subjects. Because the placebo group was never exposed to abatacept in the ST Period, these results suggest that the assay may over-predict the actual rate of immunogenicity.

In Study IM101332 the rates of immunogenicity were similar in the presence or absence of MTX and the rate of immunogenicity was also similar to the rates seen in the presence or absence of MTX in RA, as shown in Study IM101226 in MTX naive subjects with RA treated with abatacept 125 mg weekly.

Table 61 - 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

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In the Cumulative Abatacept Period, all subjects originally randomized to placebo were transitioned to weekly SC abatacept treatment. Anti-abatacept antibodies directed at both CTLA4/possibly IgG regions and IgG and/or junction regions were noted at similar frequencies for subjects randomized originally to abatacept or to placebo (see Table 62). During the post-treatment period, only reactivity against CTLA4/possibly IgG regions was detected. A higher proportion of subjects had anti-abatacept antibodies detected during the post-treatment period than during the on-treatment period.

Table 62 - 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%)

Effect of Immunogenicity on PK

Study IM101158

Among the 3 subjects with anti-abatacept antibodies, 2 subjects demonstrated ADA on Day 169 only while the third subject demonstrated seroposivity at 2 follow-up post-treatment visits only. The trough concentrations over time of the 2 subjects with on-treatment ADA at Day 169 show that concentrations remained consistent before and at the presence of ADA. Therefore, there is no effect of immunogenicity on PK. The individual profiles for Cmin over time show that concentrations remained consistent before and after the presence of positive ADA and the presence of anti-abatacept antibody reactivity did not appear to consistently affect abatacept Cmin values.

Study IM101332

Of the 8 positive subjects in the short term period, 7 subjects had trough concentrations available. The individual profiles for Cmin over time shows that concentrations remained consistent before and after the presence of ADA in the cumulative. Therefore, the presence of positive immune responses did not appear to consistently affect abatacept Cmin values.

Additionally to further assess the effect of immunogenicity on the PK of abatacept, the effect of antibody response on the clearance of abatacept was evaluated. Population PK derived estimates for clearance were combined from studies IM101158 and IM101332 and categorized by antibody response. The

distribution of clearance appears to be comparable between subjects with and without an antibody response, suggesting that immunogenicity had little to no impact on the clearance of abatacept following IV or SC administration.

Post marketing experience

Abatacept is marketed 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.

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

A review of all safety and efficacy data/information currently available for abatacept for the above mentioned indications, including review of safety signals, did not reveal a change to the established benefit-risk profile of abatacept in the approved indications.

2.5.1. Discussion on clinical safety

Orencia (abatacept, BMS-188667) administered intravenously (IV) or subcutaneously (SC) is approved for the treatment of rheumatoid arthritis (RA) in adults. Abatacept IV is also approved for the treatment of polyarticular juvenile idiopathic arthritis (JIA) in pediatric patients 6 years of age and older. The safety profile of abatacept is well established for adults with RA, including long-term follow-up. The safety profile is characterised by several potentially serious consequences, including but not limited to the identified risk of infections and potential risks of malignancies, autoimmune disorders, local injection site reactions and immunogenicity, which were also monitored during the clinical studies in psoriatic arthritis (PsA).

The safety data for patients with active PsA is derived from 2 clinical studies: IM101332, a pivotal Phase 3 study of SC abatacept and IM101158, a Phase 2b study of IV abatacept. A total of 594 subjects with active PsA were treated in the 2 clinical studies; 341 subjects received abatacept and 253 subjects received placebo during the ST period. After the ST period, all subjects received open-label (OL) abatacept in order to assess the long term safety of abatacept in subjects with PsA. Study IM101158 was terminated prematurely by the MAH due to the modest efficacy on skin-related parameters. Safety data are presented separately for each study and no formal comparison of safety data were made between treatments or studies and no formal statistical testing was performed. This is acceptable due to the different pharmaceutical forms (IV and SC) and the different definitions of some AEs in each study. AEs of special interest, i.e., infections, malignancies, autoimmune events, local site reactions, acute infusion reactions, peri-infusional reactions and AEs within 24 h of injection are discussed separately.

Since August 15th 1995, approximately 10,771 patients have been exposed to abatacept in sponsored clinical trials and the cumulative number of patients treated as of 30-Sep-2015 is estimated to be 383,451. Currently abatacept is used in combination with methotrexate (MTX) for the treatment of RA and JIA. The established a safety profile of abatacept is mainly based on data on adults with RA. In Study IM101158 the mean duration of exposure in the ST period ranged from 153.6 to 166.8 days. During the combined ST + LT period, the overall mean duration of exposure to abatacept was 20.4 months (n=161). In Study IM101332 the median days (SD) of exposure in the abatacept and placebo groups in the ST period were 147.7 days (30.5) and 140.3 days (30.0), respectively. Up to Year 2, the mean duration of

exposure to abatacept was 17.0 months for the cumulative abatacept period, and the mean number of injections was 63.2.

Adverse events

AEs were reported in comparable proportions of subjects treated with abatacept and placebo. Although, the number of treatment-related AEs was slightly higher in the abatacept-treated subjects than in the placebo treated patients.

Infections

Overall in both studies, infections were the most common AEs in both abatacept and placebo groups, however discontinuation of the treatment due to AEs of infection was only seen in the abatacept treated patients. In study IM101158 infections were reported in similar manner for both abatacept (34.9, 35% and 35.6%) and placebo (35.7%) groups. The most common AEs of infections were nasopharyngitis and other non-serious upper respiratory tract infections and bronchitis. AEs during the ST period were mild or moderate in severity, except for 1 event of very severe osteomyelitis in the abatacept 30/10 mg/kg group, which led to discontinuation of the treatment drug. A case of osteomyelitis was also reported in study IM101332. The SAEs of infection reported during the LT period in IM101158: herpes zoster, pyelonephritis acute, pneumonia and cellulitis, are already addressed in the SmPC in section 4.8 and no new safety concerns arise from these cases.

In Study IM101332 during the ST period Infections and infestations were the most commonly reported AEs. The most common infections nasopharyngitis and upper respiratory tract infections were reported slightly more often in the placebo group.

In abatacept group a case of opportunistic infection caused by Pneumocystis jirovecii was seen on one patient and leading to discontinuation of the treatment. The case of *Pneumocystis jirovecii* was further discussed. A search performed from a database for RA patients "Studies of Abatacept in Psoriatic arthritis and in Integrated Clinical Safety Database in Rheumatoid Arthritis" did not reveal additional cases. Taken into account that in the case of the AE of *Pneumocystis jirovecii* infection in Study IM101332 there were also several factors predisposing the subject to an opportunistic infection, the existing precautionary statements in SmPC Section 4.4 and the paragraph concerning infections in the SmPC Section 4.8 are considered sufficient to minimize the risk.

During the Cumulative Abatacept period up to year 2 infections and infestations were reported in 45.5% of the subjects. The most common infections reported were upper respiratory infections, bronchitis and nasopharyngitis and the treatment was discontinued due to AEs or SAEs of infection in 7 (1.8%) subjects. SAEs of infection were reported in 10 (2.5%) subjects: gastroenteritis (2 subjects) and Pneumocystis jirovecii infection during the ST period; appendicitis, Epstein-Barr virus infection, pneumonia and pyelonephritis during the OL period; and osteomyelitis, intervertebral discitis and cellulitis during the LTE.

Malignancies

Malignancies not related to skin were noted in a small proportion of abatacept-treated patients (3 subjects) and did not raise any specific safety concerns. Additionally, a total of 5 cases of skin malignancies, including precursors of malignant tumors, were reported in abatacept-treated patients in both studies.

In Study IM101158 one case of basal cell carcinoma was reported during the ST period and 3 malignancies (Bowen's disease, lentigo maligna stage unspecified, and a metastatic squamous cell carcinoma of the tongue) were reported during the LT period. The SAE of metastatic squamous cell

carcinoma of the tongue was assessed as possibly related to treatment however the subject also had a history of exposure to Agent Orange, a known carcinogen, while a soldier in the Vietnam War.

In Study IM101332 during the ST period 2 cases of malignancy were reported in placebo group (invasive ductal breast carcinoma and a B-cell lymphoma) and no malignancies were reported in the abatacept group. During the Cumulative Abatacept Period malignancies were reported in 4 subjects: a prostate cancer, a carcinoma in situ of skin, a squamous cell carcinoma of skin and a transitional cell carcinoma, which was considered related to treatment. The subject with squamous cell carcinoma had a medical history of a basal cell carcinoma of the nose.

There have been reports of NMSC in patients receiving abatacept and therefore periodic skin examination is recommended for all patients, particularly for those with risk factors for skin cancer. Patients with PsA may be at increased risk of both non-melanoma skin cancer and melanoma as they may have previous treatments with e.g. non-biological and biological DMARDs and phototherapy.

The risk of skin malignancies in PsA patients was further discussed. Overall, the data provided suggests that the incidence rates of NMSC and melanoma with abatacept use are comparable to the background rates in the PsA populations, and that the incidence rates from the Study IM101332 for NMSC are similar to the presented background rates of the general population. However, the incidence rates for NMSC and melanoma in Study IM101158 for abatacept-treated and placebo-treated patients were not provided, nor did the MAH compare incidence rates between the placebo- and abatacept-treated patients in Study IM101332. This issue will be further investigated in the context of a large pharmacoepidemiology programme setting.

There are already ongoing Category 3 additional PhV activities, namely a Post-marketing Epidemiology program, aiming to provide additional data also on the potential risk of malignancies in abatacept users. The final study report will become available in the end of 2018. This program may be biased in what comes to the applicability to the PsA patient population as no psoriasis patients with possibly an increased risk of NMSC are systematically included, yet. Therefore the MAH is now planning to continue the pharmacoepidemiological safety data gathering (as new Additional Pharmacovigilance Activities; including occurrence of overall malignancies and NMSC) via the ARTIS Swedish registry and the DANBIO Danish biologics registry. These European registries collect data on biologics regardless of indication and have the ability to link to the cancer registry. Therefore, the MAH will follow up the incidence rates of NMSC and melanoma, specifically, also within this new pharmacoepidemiological registry study (see RMP section).

Autoimmune events

In study IM101332 during the ST period no autoimmune events were reported in either group. During the LTE or OL periods three cases of autoimmune disorders were reported. None of these AEs was considered related to abatacept. In study IM101158 AEs and SAEs of psoriasis or psoriatic arthropathy were reported as autoimmune disorders.

In study IM101132 the investigators were requested not to report AEs of psoriatic arthritis or psoriasis, unless the event represented a new form of psoriasis or was an SAE. Due to these different practices, the data between the studies is not fully comparable. In general, based on the data from ST periods there was no major difference in worsening of psoriasis between abatacept- or placebo-treated patients.

In study IM101158 during the LT period AEs of psoriasis were reported for 5 (3.4%) subjects. For one subject the AE was assessed as serious. All 5 cases were assessed as unlikely or not related to study treatment and related to the underlying disease, and the treatment was continued.

During the Cumulative Abatacept period in study IM101132, AEs of psoriasis or psoriatic arthropathy were reported in a total of 8 subjects: During the OL period a SAEs of psoriatic arthropathy in 2 subjects and an AE of psoriasis, a SAE of psoriasis, an AE of skin plaque psoriasis and a SAE of erythrodermic psoriasis in one patient, each, and during the LTE 2 SAEs of psoriatic arthropathy. 3 subjects (an AE of psoriasis, a SAE of psoriasis and a SAE of erythrodermic psoriasis) discontinued abatacept therapy due to lack of efficacy and one subject discontinued due to an AE of skin plaque psoriasis.

The possible risk of worsening of psoriasis and psoriatic erythdodermia during abatacept treatment was further discussed. Based on the provided data it seems likely that AEs of psoriatic erythroderma and worsening of psoriasis seen in Studies IM101558 and IM101332 in patients treated with abatacept could be due to overall modest efficacy of abatacept on skin lesions and in the specific case of erythrodermic psoriasis, which led to hospitalization, also due to poorly controlled disease at baseline and the use of a known trigger, a high-dose corticosteroid treatment followed with a rapid withdrawal.

Infusional AEs and injection site reactions

Data related to infusional AEs and injection site reactions or Adverse Events within 24 Hours of Study Drug Administration do not raise new safety concerns. One severe anaphylactic reaction in the abatacept group was reported. The risk of anaphylaxis and anaphylactoid reaction is already identified in the safety profile of abatacept and hypersensitivity is listed in the SmPC as an uncommon AE.

Serious adverse event/deaths/other significant events

No deaths were reported in Studies IM101158 and IM101332.

In Study IM101158, during the ST period SAEs were reported in 4 (9.3%), 2 (5%), 0 and 1 (2%) subjects in abatacept 30/10, 10/10, 3/3 and placebo groups, respectively.

A SAE of cardiac failure in one subject (ST cohort: abatacept 10/10 mg/kg) was assessed as possibly related to treatment. Overall, SAEs in SOC Cardiac disorders were reported in 4 subjects (2.5 %), including atrial fibrillation in 2 subjects (1.2%) and acute coronary syndrome, aortic valve incompetence and cardiac failure each once (0.6%). In study IM101332 for Cumulative Abatacept Population up to year 2 SAEs of SOC Cardiac disorders were reported in 3 subjects. The MAH has provided further discussion on these cases in relation to abatacept including post-marketing data from RA patients during abatacept treatment. The MAH will continue to monitor cases of cardiac events in patients receiving abatacept by means of routine pharmacovigilance.

In Study IM101332 SAEs were reported in 6 (2.8%) subjects in the abatacept group and 9 (4.3%) subjects in the placebo group during the ST period. SAEs considered treatment-related were reported in 1 (0.5%) subject in each group: *Pneumocystis jirovecii* infection in the abatacept group and increased ALT in the placebo group. 2 malignancies were reported, both in the placebo group.

Overall across both studies AEs or SAEs of osteonecrosis were reported in 3 subjects. An additional search from the Integrated Clinical Safety Database in Patients with RA was performed. The search identified five (5) events of osteonecrosis reported in the double-blind, placebo-controlled RA studies of which four (4) of the cases were receiving abatacept treatment with a frequency of 0.2% and 1 case receiving placebo with a frequency of 0.1%. A further evaluation of the cases identified in studies IM101158 and IM1011332 revealed that a case of osteonecrosis reported in Study IM101158, was actually a sequelae of osteoarthritis and in another case corticosteroid use was identified as a risk factor. One case remained without known predisposing risk factors, but raises no further safety concern.

Laboratory findings

In general markedly abnormal laboratory values were uncommon and majority of these findings in laboratory values are fairly common in PsA population with comorbidities such as metabolic syndrome and type II diabetes. Majority of the subjects with high levels of blood glucose had a medical history that included diabetes mellitus: 9/16 (56.3%) subjects during ST and/or LT in study IM101558 and 14/20 (70.0%) subjects during the Cumulative Abatacept Period up to year 1 in IM101332.

In study IM101332 low and high levels of blood glucose and elevated fasting triglycerides were observed both in abatacept- and placebo-treated subjects.

In study IM101558 lipid tests were not performed, but high and low levels of blood glucose were also observed both in abatacept- and placebo-treated subjects. It is noteworthy that mean reductions from baseline at Day 169 in serum IgA, IgG, and IgM were noted in the 3 abatacept groups but not in the placebo group. Reduced numbers of immunoglobulins IgG, IgA, and IgM have also been previously noted in association with abatacept in studies in RA population.

Patients with psoriatic arthritis may potentially have wide-spread areas of skin affected by psoriasis, i.e., lesions of skin that have lost the protective skin barrier predisposing these patients to infection.

Abatacept modulates T cell costimulation and it interferes with the activation of T cells and their ability to provide help to B cells, although no clear relationship of abatacept treatment with lymphopenia could be established as lymphopenia also occurred in the placebo group. Mean reductions from baseline in immunoglobulins were generally less than 10% with abatacept treatment and this finding was considered to have only minimal impact. Nevertheless, immune suppression, such as caused by abatacept, associated with therapies for psoriasis may diminish the ability to control an infection. If the treatment has the potential to heal lesional skin in psoriasis, it could theoretically be subverting the immune machinery necessary to fight infections.

SAEs of infection or discontinuation of the treatment due to AEs of infection were seen more often among abatacept-treated patients. Also some events of SAEs of infection were ongoing at the time of database lock and the treatment remained interrupted and discontinuation of the treatment was not recorded. In conclusion, PsA patients should be carefully monitored for possible infections during treatment with abatacept (see warning in section 4.4 of the SmPC). In patients with severe skin disease the risk for serious infections may be further increased.

No subgroup analyses of safety were performed in IM101158. In Study IM101332 no clinically relevant differences in safety were seen in subgroup analyses by age (< 65 years old, 65 years old), baseline weight (60-100 kg, > 100 kg), gender (male, female), geographic region (North America, Europe, South America, ROW), MTX use at Day 1 (yes, no), TNFi-exposed (yes, no).

Immunogenicity (Immunological events)

In Study IM101158, ADA were reported for 1/43 (2.3%), 0/40 (0), and 2/45 (4.4%) subjects in the IV abatacept 30/10 mg/kg, 10/10 mg/kg, and 3/3 mg/kg groups, respectively. Serum samples from placebo group were not analysed. None of these subjects had AEs potentially related to immunogenicity. In the LT period, on-treatment immunogenicity rate ranged from 0 to 5.9% and the post-treatment immunogenicity rate from 3.1% to 8.0% in the abatacept groups. All these ADAs were directed to the "CTLA4 and possibly Ig" portion.

In study IM101332, 8/203 (3.9%) of abatacept-treated subjects and 17/198 (8.6%) of placebo-treated subjects had on-treatment ADAs during the Short-term Period, with the majority of these directed against the IgG portion of the molecule. Immunogenicity detected in the placebo-treated patients suggests that the assay may over-predict the actual rate of immunogenicity.

The proportion of patients with ADA at 28d, 85d and 168d post last dose was high, i.e. 14%, 60% and 75%, respectively, (overall 37,5%), however the number of subjects tested was very small (7, 5 and 4, respectively). The high ADA-prevalence during the post-treatment period is consistent with the known immunogenicity profile in RA and is probably due to immunomodulatory effects of abatacept for anti-abatacept antibody formation during the treatment.

Several factors, such as a conservative setting of both screening and confirmation assays as well as the strict definition of positive relative to baseline may have contributed to the over-prediction of immunogenicity. Prior exposure to immunoglobulin containing products, including biologics and blood transfusions may also explain the high incidence of reactivity.

Overall, the number of subjects evaluated for immunogenicity by the ECL assay in the abatacept group (203 subjects) and placebo group (198 subjects) were similar in the ST Period. At baseline in the abatacept group, 23/203 (11.3%) all subjects had IgG specificity and in the placebo group, 19/198 (9.6%) all except one had IgG specificity and only one with specificity to CTLA4 and a relatively low titer. The immunogenicity rates in the placebo group (17/198, 8.6%) were comparable to the rates of preexisting reactivity observed in the baseline samples seen in abatacept group (23/203 (11.3%)). From the subjects who tested positive in the baseline in the abatacept group, 3/203 (1.47%) tested positive for "CTLA4 and possibly Ig" and 5/203 (2.46%) for "Ig and/or junctional region". In the placebo group, 3/198 (1.51%) tested positive for "CTLA4 and possibly Ig" and 14/198 (7.07%) tested positive for "Ig and/or junctional region".

The results show that the assay may in fact over-predict the true frequency of ADAs, especially against the IgG region. Prior exposure to immunoglobulin containing products, including biologics and blood transfusions may also explain the high incidence of reactivity. However, the presented data overall suggests that even with the strict definition of ADA positivity relative to baseline, antibody response does not have a clear impact on PK, safety or efficacy. Currently abatacept is indicated in combination with methotrexate for the treatment of RA in adults and for JIA in paediatric patients 6 years of age. The effect of MTX was assessed in study IM101332 and the rate of immunogenicity was found to be similar in the presence or absence of MTX, and consistent with the rates seen before in the presence or absence of MTX in RA. In conclusion, the data provided do not suggest that MTX use would have an effect on the formation of ADAs.

In studies IM101332 and IM101158 the individual profiles for C_{min} over time showed that concentrations remained consistent before and after the presence of positive ADA, and the presence of anti-abatacept antibody reactivity did not appear to consistently affect abatacept C_{min} values. Graphical exploration of the data indicated that clinically meaningful effect of ADA on pharmacokinetics of abatacept in PsA patients is unlikely. Overall, the data related to anti-abatacept antibodies in studies IM101158 and IM101332 show consistency with the known immunogenicity profile of abatacept in RA.

2.5.2. Conclusions on clinical safety

The safety profile including the type and the incidence of adverse events, SAEs and immunogenicity in patients with PSA is in general consistent with that seen earlier in patients with RA.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 23.0 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

Safety concerns

Summary of safety concerns	

Important identified risks	• Infections with special reference to TB and patients with COPD
	• Infusion-related reactions (IV abatacept only)
	• Injection reactions (SC abatacept only)
	  • Prefilled Syringe
	  • Autoinjector

Important potential risks	• Malignancies, with special reference to lymphoma, NMSC, lung cancer, and breast cancer
	• Autoimmune symptoms and disorders
	• Immunogenicity
	• Pregnancy
	• PML
	• Administration error (SC abatacept only)
	  • Prefilled Syringe
	  • Autoinjector
	• Infections associated to immunization with live vaccines

Missing information	• Hepatic and renal impairment • Combination therapy including biologic therapy • Elderly subjects

Pharmacovigilance plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
Safety of DMARD and Biologic Treatment of Rheumatoid Arthritis (IM101045A) *(non-interventional cohort, 3*	To estimate incidence of targeted infections in hospitalized patients exposed to abatacept (IV & SC) vs. patients exposed to DMARDs & biologics; exploratory analyses of pediatric and off-label use	Infections, infusion-related reactions, autoimmune disorders, injection reactions, combination biologic use, elderly	Ongoing	Interim data submitted each Feb in summary report Final Study Report: Dec-2016
Observational Cohort to Assess Safety and Outcomes in Patients Treated with Abatacept	To assess risk of infections, malignancies, and mortality in patients	Infections, infusion-related reactions, malignancies,	Ongoing	Interim data submitted each Feb in summary report

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
and Other Anti-Rheumatic Therapies (IM101045B) (*non-interventional cohort, 3)*	initiating abatacept vs. patients adding or switching to biologics & DMARDs	autoimmune disorders, pregnancy, injection reactions, combination biologic use, elderly		Final Study Report: Dec-2016
Abatacept Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project An Extension Study (IM101121) *(non-interventional cohort, 3)*	To estimate risk of major congenital anomalies/birth defect patterns in offspring of patients exposed to abatacept during pregnancy	Pregnancy	Ongoing	Interim data submitted each Feb in summary report Final Study Report: Dec-2018
A Nationwide Post-Marketing Study on the Safety of Abatacept Treatment in Sweden Using the ARTIS Register (IM101125) *(non-interventional cohort, 3)*	To assess short- and long-term SAEs and mortality among patients exposed to abatacept vs. other biologics, and DMARDs	Infections, infusion-related reactions, malignancies, autoimmune disorders, pregnancy, PML, injection reactions, elderly	Ongoing	Interim data submitted each Feb in summary report Final Study Report: Dec-2018
Long-Term Observation of Treatment with Biologics in Rheumatoid Arthritis RABBIT (IM101127) *(non-interventional cohort, 3)*	To assess short- and long-term safety (AEs) and mortality among registry patients exposed to abatacept vs. other biologics, DMARDs	Infections, infusion-related reactions, malignancies, autoimmune disorders, pregnancy, PML, injection reactions, elderly	Ongoing	Interim data submitted each Feb in summary report Final Study Report: Dec-2018
Post-Marketing Observational Study Assessing the Long-Term Safety of Abatacept Using the DREAM Database in the Netherlands (IM101212) *(non-interventional cohort, 3)*	Characterize abatacept patients' demographics, medical and drug history, estimate incidence of infections, malignancies, mortality in patients receiving abatacept vs. non-biologic DMARDs	Infections, malignancies, mortality	Ongoing	Interim data submitted annually Final Study Report: Dec-2018
Post-Marketing Observational Study Assessing the Long-Term Safety of Abatacept Using a Population-Based Cohort of Rheumatoid Arthritis Patients in the Province of British Columbia (IM101213) *(non-interventional cohort, 3)*	To estimate incidence of infections, malignancies, mortality, and multiple sclerosis in abatacept exposed patients vs. patients exposed to DMARDs & biologics	Infections, malignancies, autoimmune disorders (MS), combination biologic use, elderly	Ongoing	Interim data submitted each Feb in summary report Final Study Report: Dec-2018
Multinational Surveillance of Abatacept-Treated Patients During Disease Registries (IM101211) *(non-interventional*	To assess abatacept patient demographics and incidence of malignancies, infections, infusion	Infections, infusion-related reactions, malignancies, autoimmune	Ongoing	Interim data submitted each Feb in summary report Final Study Report:

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
cohort, 3)	reactions, autoimmune events and mortality	disorders, elderly		Dec-2018
An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis (IM101240) *(non-interventional cohort, 3)*	To characterize and evaluate the safety of abatacept in JIA in routine clinical practice: infections, malignancy, autoimmune disorders	Infections, infusion-related reactions, malignancies, autoimmune disorders, immunogenicity, pregnancy	Ongoing	Recruiting Update: Annually each Feb beginning in 2011 Interim Study Report: 30-Jun-2014 30-Jun-2019 30-Jun-2024 Final Study Report: no later than 30-Jun-2029

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified Risks		
Infections TB Patients with COPD	Specific subsections on infections and/or ADRs in subjects with COPD in Sections 4.3, 4.4, and 4.8 of the SmPC	Patient Alert Card: the card highlights the need for an adequate history and screening related to infections, such as TB and hepatitis, prior to treatment with abatacept, as well as the need to seek immediate medical attention when symptoms of infections occur during treatment.
Infusion-related reactions (IV abatacept only)	Specific subsections on allergic or infusion-related reactions in Sections 4.3, 4.4 and 4.8 of the SmPC.	Patient Alert Card: the Card highlights risk of hypersensitivity after use of abatacept and instructs patients to seek immediate medical attention should symptoms of serious hypersensitivity develop.
Injection reactions (SC abatacept only, both prefilled syringe and autoinjector)	Specific subsections on allergic or injection reactions in Sections 4.3, 4.4 and 4.8 of the SmPC.	Patient Alert Card: the Card highlights risk of hypersensitivity after use of abatacept and instructs patients to seek immediate medical attention should symptoms of serious hypersensitivity develop.
Potential Risks		
Malignancies Lymphoma NMSC Lung cancer Breast cancer	Specific subsections on malignancies in Sections 4.4 and 4.8 of the SmPC.	Not applicable
Induction/exacerbation of autoimmune disease	Specific subsections on autoimmune disease or autoantibodies in Sections 4.4 and 4.8 of the SmPC.	Not applicable
Immunogenicity	Specific subsection on immunogenicity in Section 4.8 of the SmPC	Not applicable
Effects during pregnancy	Pregnancy related information available in sections 4.6 and 5.3	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	of the SmPC	
PML	Specific subsection on PML in Section 4.4 of the SmPC	Not applicable
Administration error (SC abatacept only, both prefilled syringe and autoinjector)	Instructions for SC administration are provided in the Posology and method of administration section of the SmPC and detailed instructions for patients on administration techniques are provided in the PIL of the SmPC	Not applicable
Infections associated to immunization with live vaccines	SmPC specific subsections in sections 4.4, 4.5 and 4.6 on vaccinations and use of live vaccines in newborns and infants.	Patient Alert Card highlights the need to inform a child's physician before any vaccination is given if the child was exposed to ORENCIA in utero
Missing information		
Hepatic and renal impairment	Section 4.2 of the SmPC indicates that abatacept has not been studied in this subject population and that no dose recommendations can be made	Not applicable
Combination therapy	Subsections on combination therapy in Sections 4.4 and 4.5 of the SmPC	Not applicable
Elderly population	Statements on the use of abatacept in the elderly in Sections 4.4 and 4.8 of the SmPC	Not applicable

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Croatia (Hrvatska).

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- Consultation with target patient groups on the Package Leaflet has been performed at the occasion of the original Marketing Authorization Application of ORENCIA powder for concentrate for solution for infusion for the treatment of Rheumatoid Arthritis (EC Decision received on 21 May 2007).
- The readability of the ORENCIA solution for injection Package Leaflet has been tested at the occasion of the Extension Application for this second pharmaceutical form and route of administration (EC Decision received on 4 October 2012).

- A bridging report to validate a US conducted User Testing for the "Instructions for Use" portion of the package leaflet was submitted and approved for the Orencia solution for injection in pre-filled pen (CHMP opinion on 23 April 2015).
- Only limited changes (i.e. those relevant to the new indication) are made to the Package Leaflet, the routes of administration and the safety profile remain the same.
- Administration of ORENCIA powder for concentrate for solution for infusion is done by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL remain unchanged.
- The general design and layout of the proposed PL has not changed compared to the tested ones.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

ORENCIA, alone or in combination with methotrexate, 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.

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) 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.

More than half of patients with PsA exhibit progressive, erosive arthritis that often is associated with functional impairment. 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.

3.1.2. Available therapies and unmet medical need

TNFi agents were the first biologic agents approved for the treatment of PsA. Ustekinumab, an inhibitor of IL-12/23, apremilast, an inhibitor of PDE4, and secukinumab, an antibody directed against IL-17, were also recently approved for PsA. These 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 (ie, ACR 20) based on clinical trial data. In addition, TNFi-exposed patients may be more resistant to treatment, as the proportion of subjects achieving an ACR 20 was lower for TNFi-exposed than in TNFi-naive subjects in trials of ustekinumab, apremilast, and secukinumab.

3.1.3. Main clinical studies

The application is based on data from a supportive Phase 2b study with abatacept administered IV (IM101158) and a pivotal Phase 3 study with abatacept administered SC (IM101332). In both studies abatacept was compared to placebo in a 6-month, double-blind, short-term period, followed by an open-label long-term period. The long-term period of Study IM101332 is ongoing.

3.2. Favourable effects

The phase 2b study of IV abatacept (IM101158) and the pivotal phase 3 study of SC abatacept (IM101332) included subjects with PsA and psoriasis. The primary efficacy endpoint was achieved in both studies as significantly higher proportion of abatacept-treated subjects compared to placebo-treated subjects met the ACR 20 response criteria at Day 169. In Study IM101158, ACR 20 response rate at Day 169 was similar for abatacept 30/10 mg/kg (41.9%) and abatacept 10/10 mg/kg (47.5%) treatment groups and significantly higher in comparison to placebo group (19.0%; p = 0.022 and 0.006, respectively). In Study IM101332, significantly higher proportion of subjects in the abatacept group compared to the placebo group met the ACR 20 response criteria at Day 169 (39.4% vs. 22.3%, respectively, p <0.001).

Among the secondary efficacy endpoints related to signs and symptoms of PsA, subjects treated with abatacept in Study IM101158 demonstrated greater improvement at Day 169 in the physical component of SF-36 in comparison to subjects treated with placebo, with the highest adjusted differences from placebo of 9.12 in the abatacept 10/10 mg/kg group. The 95% CIs for each comparison to placebo did not contain zero. Some improvement was also seen in the mental component of SF-36 but all 95% CIs for the adjusted differences contained zero. The estimated differences from placebo in the HAQ-DI scores were 16.0%, 26.1%, and 16.6% for the abatacept 30/10 mg/kg, 10/10 mg/kg, and 3/3 mg/kg groups, respectively, and for the abatacept 10/10 mg/kg group the 95% CI did not contain zero.

In Study IM101332, among key secondary endpoints, the proportion of HAQ responders was numerically higher in the abatacept group compared to the placebo group but was not statistically significant (31.0% vs. 23.7%, respectively, p=0.097). Since the analysis of HAQ-response showed statistically non-significant result, treatment differences for endpoints lower in the testing hierarchy (i.e., ACR 20 response rate at Day 169 in the TNFi-naive and the TNFi-exposed cohorts and x-ray non-progressor rate at Day 169) could not be tested for significance and statistical claims for the presented nominal p-values could not be made. Among the key secondary endpoints, higher proportion of subjects in the abatacept group met the ACR 20 response criteria at Day 169 in both the TNFi-naive and TNFi-exposed subpopulations (44.0% and 36.4%, respectively) compared to the placebo group (22.2% and 22.3%, respectively; nominal p-values 0.003 and 0.012, respectively; and the 95% CIs for the estimates of difference did not contain zero). There was also a higher proportion of radiographic non-progressors at Day 169 in the abatacept group compared to the placebo group (42.7% vs. 32.7%; nominal p-value=0.034; the 95% CI for the estimate of difference did not contain zero). Based on the data available up to one year, it can be concluded that abatacept treatment has a beneficial effect on joint structure.

In the long term treatment up to one year, the effects of IV and SC abatacept were maintained.

3.3. Uncertainties and limitations about favourable effects

While the efficacy of IV and SC abatacept based on the primary efficacy endpoint was demonstrated, results of the secondary efficacy endpoints only partially supported the primary efficacy analysis. In Study IM101332, the proportion of HAQ responders was not statistically significant and statistical claims for the nominal p-values for endpoints lower in the testing hierarchy could not be made. Consequently, results related to ACR 20 response rate at Day 169 in the TNFi-naive and the TNFi-exposed cohorts and x-ray non-progressor rate at Day 169 are descriptive only. There was also no clinically relevant effect of abatacept on skin symptoms.

3.4. Unfavourable effects

In both studies, infections were the most common AEs in both abatacept and placebo groups during the double-blind period and remained the predominant AEs across the reporting period. In study IM101332 during the Cumulative Abatacept period up to year 2 infections and infestations were reported in 52.5% of the subjects and in study IM101158 in the All Treated Subjects in LT Period population in 56.5% of the subjects.

Malignancies not related to skin were reported in a total of 3 subjects. Additionally, skin malignancies, including precursors of malignant tumors, were reported in 5 abatacept-treated patients across both studies.

Among laboratory findings, lymphopenia and lower levels of immunoglobulins were noted in the abatacept group. In Study IM101158, mean reductions from baseline in serum IgA, IgG, and IgM were noted in the 3 abatacept groups but not in the placebo group.

3.5. Uncertainties and limitations about unfavourable effects

In relation with the reported malignancies and precursors of malignant tumors of the skin, it should be noted that patients with PsA may be at increased risk of both non-melanoma skin cancer and melanoma, as these patients have previous treatments with non-biological and biological DMARDs and phototherapy. Malignancies, including NMSC, are an important potential risk for abatacept, as outlined in the RMP. However, the patient numbers in the PsA studies are very small and therefore no definitive conclusions can be drawn. There are ongoing Category 3 additional PhV activities, namely Epidemiology program, aimed to provide additional data also on the potential risk of malignancies in abatacept users.

Potentially, the effect of abatacept on T-cells and on B-cells, causing lymphopenia and reduced number of immunoglobulins may predispose PsA patients to serious infections, appropriate warnings and recommendations are already in place in the SmPC.

It remains unclear if the neutralising antibody assay is fully suitable for its intended purpose, as drug interference occurred at abatacept levels relevant for PsA patients and thus only half of the samples could be properly analyzed. CHMP recommended that for any future application for Orencia containing immunogenicity assessment the MAH will improve the Nab assay, particularly the drug tolerance for abatacept levels more relevant in patients' sera.

3.6. Effects Table

Table 63 - Effects Table for Orencia in PsA

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
ACR 20 response at Day 169	Primary endpoint in Study IM101158: Efficacy of three regimens of IV abatacept (30/10 mg/kg, 10/10 mg/kg,	%	Abatacept IV 30/10 mg/kg: 41.9% abatacept IV 10/10 mg/kg: 47.5% Comparison to	Placebo: 19.0%	Statistically significant but clinically modest level of efficacy

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
	and 3/3 mg/kg) vs placebo		placebo: p = 0.022 and 0.006		
ACR 20 response at Day 169	Primary endpoint in Study IM101332: Efficacy of SC abatacept125 mg vs placebo	%	Abatacept SC: 39.4% Comparison to placebo: p <0.001	Placebo: 22.3%	Statistically significant but clinically modest level of efficacy
ACR 20 response at Day 169 in the TNFi-naive and the TNFi-exposed cohorts	Key secondary endpoints in Study IM101332: Efficacy of SC abatacept 125 mg vs placebo	%	Abatacept SC in TNFi-naive and -exposed cohorts: 44.0% and 36.4% Comparison to placebo: nominal p-values 0.003 and 0.012	Placebo: 22.2% and 22.3%	Higher proportion of subjects in the SC abatacept group met the response criteria in both subpopulations. No statistical claims for the presented nominal p-values can be made but the 95% CIs for the estimates of difference did not contain zero
SF-36, HAQ-DI, proportion of radiographic non-progressors at Day 169	Joint-related secondary endpoints in Studies IM101158 and IM101332		Abatacept IV and SC	Placebo	Results of the secondary efficacy endpoints related to the joint disease only partially supported the primary efficacy analysis (see Table 44 and Table 45: Summary of Efficacy for trial)
IGA Score, Target Lesion Score, PASI 50, PASI 70	Skin-related endpoints in Studies IM101158 and IM101332		Abatacept IV and SC	Placebo	No clinically relevant or statistically significant effect of abatacept vs placebo (see Table 44 and Table 45: Summary of Efficacy for trial)
Unfavourable Effects					
AEs in study IM101158	ST period	%	Abatacept IV 30/10:67.4% Infections: 34.9% Malignancies: 2.3%Abatacept IV 10/10: 77.5% Infections: 35.0% Malignancies: 0% Abatacept IV 3/3: 68.9% Infections: 35.6% Malignancies: 0%	placebo: 71.4% Infections: 35.7% Malignancies: 0%	Similar number of AEs between the treatment groups
AEs in study IM101132	ST period	%	Abatacept SC: 54.5%	placebo: 53.1%	Similar number of AEs between the treatment

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
			Infections: 26.8% Malignancies: 0%	Infections: 29.9% Malignancies: 0.9%	groups
SAEs in study IM101158	ST period	n (%)	Abatacept IV 30/10: 4 (9.3%) 10/10: 2 (5%) 3/3: 0 (0%)	placebo: 1 (2%)	
SAEs in study IM101132	ST period	n (%)	Abatacept SC: 6 (2.8%)	placebo: 9 (4.3%)	
Immungenicity in study IM101158	ST period	n (%)	Abatacept IV 30/10: 1/43 (2.3%) 10/10: 2/40 (0%) 3/3: 0 (0%)	placebo: N/A	Serum samples from placebo-group were not analysed
Immungenicity in study IM101132	ST period	n (%)	Abatacept SC: 8/203 (3.9%)	placebo: 17/198 (8.6%)	
ADAs in study IM101158	LT period	n (%)	On-treatment: 0 (0/42) - 5.9% (2/34) Post-treatment: 3.1% (1/32) - 8.0% (2/25)		
ADAs in study IM101132	Post-last dose	%	28d: 14% 85d: 60% 168d: 75% overall: 37,5%		High number of patients with post-treatment ADAS. However, only few patients tested (7,5 and 4 respectively).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy of IV and SC abatacept based on the primary efficacy endpoint was demonstrated, as statistically significantly higher proportion of abatacept-treated subjects compared to placebo-treated subjects met the ACR 20 response criteria at Day 169. Results of the secondary efficacy endpoints related to the joint disease, however, only partially supported the primary efficacy analysis, and no clinically relevant or statistically significant effect on skin parameters was demonstrated.

The population in the abatacept PsA studies was similar to that in pivotal studies of other biological DMARDs but Study IM101332 included more treatment-resistant patients: The proportion of subjects exposed to prior TNFi therapy was 61.1%, and 17.2% were exposed to more than one prior TNFi therapy.

Efficacy of abatacept was shown in this population but formal statistical significance testing is lacking for both IV and SC abatacept.

Psoriasis is a one of the key manifestations of PsA, and current psoriasis or personal or family history of psoriasis is a keystone of the CASPAR criteria for PsA. There was no clinically relevant effect of abatacept on psoriasis and therefore abatacept is unsuitable for patients who require systemic therapy for psoriatic skin lesions and the indication has been updated accordingly.

The safety profile, including the type and incidence of adverse events, SAEs and immunogenicity is in general consistent with that seen earlier in patients with RA.

3.7.2. Balance of benefits and risks

Efficacy of abatacept by prior and concomitant MTX has been sufficiently demonstrated. ACR 20 responses in the subgroups by prior TNFi exposure, with or without MTX, consistently showed improvement relative to placebo, and higher response rates in the anti-TNF naïve patients were seen. In conclusion, treatment with or without MTX is considered acceptable. However, data on treatment with or without nbDMARD are too limited to allow such recommendation. Therefore the wording of the indication was changed to: "*ORENCIA can be used alone or in combination with ~~non-biological DMARDs~~**MTX***".

With regard to the target population, it is agreed that benefit of IV and SC abatacept has been demonstrated in PsA population in both second-line (DMARD-IR) and third-line (TNFi-IR) treatment. The efficacy was clinically relevant but rather modest, which is partly explained by the relatively slow onset of action of abatacept and the design of Study IM101332 with early and stringent escape option.

There was no clinically relevant effect of abatacept on skin symptoms. Therefore abatacept seems unsuitable for the treatment of PsA in patients with moderate to severe psoriasis. Therefore, the indication wording excludes patients that require additional systemic therapy for psoriasis. Of importance, there were rather few discontinuations due to lack of skin efficacy and no emergence of e.g. pustular psoriasis was observed.

The Benefit-Risk balance of Orencia is positive in the treatment of PsA after previous DMARD therapy, i.e., in both second- and third-line patients, when additional systemic therapy for psoriatic skin symptoms is not required.

3.8. Conclusions

The overall B/R of Orencia is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of psoriatic arthritis in adults; as a consequence sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. A revised RMP was agreed (version 23).