EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/639090/2016
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Orencia

International non-proprietary name: abatacept

Procedure No. EMEA/H/C/000701/II/0097

Marketing authorisation holder (MAH): Bristol-Myers Squibb Pharma EEIG

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List of abbreviations

ABA	Abatacept
ACPA	anti-cyclic citrullinated peptide antibody
ACR	American College of Rheumatology criteria for improvement
ACR20	ACR criteria for 20% improvement
ACR50	ACR criteria for 50% improvement
ACR70	ACR criteria for 70% improvement
ACR90	ACR criteria for 90% improvement
AE	Adverse event
AGREE	BMS Study IM101023
Anti-CTLA4-T	antibodies directed to the CTLA4 portion of abatacept
AMPLE	BMS Study IM101235
ATTEST	BMS Study IM101043
AVERT	BMS Study IM101226
CD	Cluster of differentiation
CDAI	Clinical Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIA	chronic idiopathic arthritis
CMH	Cochran Mantel Haenszel
CRP	C reactive protein
CSR	Clinical study report
CTLA	Cytotoxic T-lymphocyte-associated protein
DAS28	Disease Activity Score 28
DMARD(s)	Disease modifying anti rheumatic drug(s)
ECL	Electrochemiluminescence
eCTD	Electronic Common Technical Document
ELISA	enzyme-linked immunosorbent assays
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FUM	Follow up measure
GI	gastrointestinal
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
hs-CRP	High sensitivity CRP
IR	Insufficient Response
ITT	Intent-to-Treat
IV	Intravenous
JIA	Juvenile idiopathic arthritis
JSN	Joint space narrowing
MA	Marketing authorisation or market abnormality
MCR	Major clinical response
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTX	Methotrexate
MTX-IR	Methotrexate-inadequate-responder
MTX-naive	Subjects not previously treated with MTX
OR	Odds ratio
PCS	Physical Component Summary
PD	pharmacodynamics
PDA	Personal Digital Assistant
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plans
PK	pharmacokinetics
PLA	Placebo
PML	progressive multifocal leukoencephalopathy
PRO	Patient-reported outcomes

PT	Preferred term
RA	Rheumatoid arthritis
RF	Rheumatoid Factor
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SF-36	Short Form (36) Health Survey
SIR	Standardized incidence ratio
SmPC	Summary of Product Characteristics
SOC	System Organ Class
STPR	Stratégies Thérapeutiques dans la Polyarthrite Rhumatoïde
TB	tuberculosis
TNF	Tumor necrosis factor
TNF-IR	Tumor necrosis factor-antagonist-inadequate responder
USA	United States of America
WPAI-RA	Work Productivity and Activity Impairment Questionnaire: Rheumatoid arthritis

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 10 November 2015 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 for Orencia in combination with methotrexate (MTX) in the treatment of adults with rheumatoid arthritis (RA) who have highly active disease with poor prognostic factors (such as ACPA+ and/or RF+, joint erosion) not previously treated with MTX. As a consequence, sections 4.1 and 5.1 of the SmPC are updated based on results from AVERT study (IM101226). The Package Leaflet is updated accordingly. Moreover, the updated RMP version 20 has been submitted.

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/100/2009 (abatacept iv use) and P/0128/2014 (abatacept sc use) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/100/2009 was completed and PIP P/0128/2014 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 MAH 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

The applicant did not seek Scientific Advice at the CHMP.

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	10 November 2015
Start of procedure:	28 November 2015
Rapporteur's preliminary assessment report circulated on:	22 January 2016
Co-Rapporteur's preliminary assessment report circulated on:	22 January 2016
PRAC Rapporteur Assessment Report	22 January 2016
PRAC members comments	3 February 2016
Updated PRAC Rapporteur Assessment Report	4 February 2016
PRAC Outcome	11 February 2016
CHMP members comments	n/a
Updated CHMP Rapporteur Joint Assessment Report	18 February 2016
Request for supplementary information and extension of timetable adopted by the CHMP on	25 February 2016
MAH's responses submitted on	19 May 2016
Restart of the procedure	23 May 2016
Rapporteur's preliminary assessment report on the MAH's responses circulated on	21 June 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	27 June 2016
PRAC members comments	29 June 2016
Updated Rapporteur's assessment report on the MAH's responses circulated on	5 July 2016
PRAC Outcome	7 July 2016
CHMP members comments	11 July 2016
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	14 July 2016
Opinion	21 July 2016

2. Scientific discussion

2.1. Introduction

The active substance of Orencia, abatacept, is a fusion protein that consists of the extracellular domain of human Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) linked to a modified Fc portion of human IgG1. Abatacept reversibly binds to CD 80/86 on antigen presenting cells via its CTLA-4 portion preventing the interaction of CD 80/86 with CD28 on T cells. This interaction provides a co-stimulatory signal necessary for full activation of T-lymphocytes. Activated T-lymphocytes are implicated in the pathogenesis of rheumatoid arthritis (RA) and are found in the synovium of patients with RA.

Orencia was initially approved in the United States of America for the treatment of adult RA patients in Dec-2005 and in the EU for intravenous (iv) administration for the treatment of moderate and severe

rheumatoid arthritis, in combination with MTX, in RA patients with an insufficient response to a TNF-alfa inhibitor (TNF-IR) in 2007. Subsequently, Orencia was authorised for the treatment of moderately to severely active JIA, in pediatric patients from 6 years of age in 2010 (EMA/H/C/00701/II-24).

In the same year the indication was extended to include adult MTX-IR RA patients (EMA/H/C/00701/II-33), which also included data on MTX-naïve patients treated with IV abatacept (AGREE study; IM101023). Study IM101023 was a 1-year phase 3 multi-centre, randomized, double-blind study to evaluate remission and joint damage progression in MTX-naïve early erosive rheumatoid arthritis subjects with abatacept plus methotrexate compared with methotrexate, with an open 1 year follow-up (where all patients received abatacept and methotrexate).

Orencia was licensed for subcutaneous (sc) administration in 2012 (EMA/H/C/00701/X-54). Based on data from clinical studies IM101235 and IM101173, a type II variation submitted in 2013 (EMA/H/C/00701/II-77), an initial abatacept iv loading dose is not required to achieve clinical efficacy with abatacept sc. Therefore, the approved posology of sc abatacept in adults with moderate to severe RA is currently 125 mg administered subcutaneously once weekly with or without an IV loading dose.

An alternative presentation Orencia pre-filled pen (autoinjector) was introduced for sc self-administration in 2015.

Currently, three TNF-inhibitors (adalimumab, etanercept and golimumab) and one interleukin six inhibitor (tocilizumab) are approved in the EU for the treatment of patients with severe, active and progressive RA not previously treated with MTX and two TNF-inhibitors (infliximab and certolizumab pegol) for patients not previously treated with MTX or other DMARDs.

Guidelines from the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), and the French Society of Rheumatologists (SFR) working group, specifically recommends the very early use (within 6 months of diagnosis) of biological therapy in patients with poor prognostic factors such as ACPA positivity, RF positivity, joint erosion, and high disease activity.

This type II variation application was initially to extend the current indication of Orencia in combination with methotrexate (MTX) to the “treatment of adult patients to patients with rheumatoid arthritis (RA) who have highly active disease with poor prognostic factors (such as ACPA+ and/or RF+, joint erosion) not previously treated with MTX.”

No amendments to the currently approved posology in adult patients were proposed with this application.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

Abatacept is a protein composed of natural amino acids and therefore is exempted from testing because of its chemical structure in accordance with the “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use” (EMEA/CHMP/SWP/4447/00).

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

In support of this type II extension of indication variation the MAH has provided the final results of a single study IM101226, the AVERT Study.

Study ID	Report Location in CTD	Study Objective	Study Design Type of Control	Formulation Dosage Regimen Route	Number of Treated Subjects	Subject Type	Duration of Treatment	Study Status Type of Report
IM101226 LT DCN 930094604	5.3.5.1	To evaluate the efficacy and safety of abatacept SC in combination with MTX in inducing clinical remission compared to MTX mono-therapy in adults with very early RA	Random-ized, Active Controlled. 12- months treatment period, followed by up to12-month withdrawal period, and 6-month re-exposure period	abatacept 125 mg/week SC + MTX; placebo SC + MTX; or abatacept 125 mg/week SC + placebo tablet	N=351 (119 - abatacept + MTX 116 - abatacept monother apy 116 MTX monother apy)	At least 18 years of age with currently active clinical synovitis of at least 2 joints (distal interphalangeal joints excluded), 1 of which must be a small joint, for at least 8 weeks at screening; had an onset of persistent symptoms of 2 years or less; had a DAS28-CRP score of ≥ 3.2 at screening; were naive or had minimum exposure to MTX (≤ 10 mg/week for ≤ 4 weeks, and no dose for at least 1 month) prior to screening and who had never received biologic therapy; were withdrawn from any treatment with chloroquine, hydroxychloroquine, and/or sulfasalazine for a minimum of 28 days prior to randomization; if treated with oral corticosteroids, were on a stable low dose (≤ 10 mg/day prednisone equivalent)	Mean months of exposure during Treatment Period: Abatacept + MTX-12.7 Abatacept monotherapy-12.4 MTX monotherapy-12.3 Mean Months of exposure during Re-exposure Period: Abatacept + MTX-6.8 Abatacept -6.8 MTX -7.1	Completed Full

In addition as supplementary evidence the MAH referred to data from study IM101023 (AGREE), which has been assessed previously EMA/H/C/00701/II-033 in 2010. This study was a 1-year phase 3 multi-centre, randomized, double-blind study to evaluate remission and joint damage progression in methotrexate-naïve early erosive rheumatoid arthritis subjects (n=509) with abatacept plus methotrexate compared with methotrexate, with an open 1 year follow-up (where all patients received abatacept and methotrexate), using the IV formulation of abatacept supports this application.

2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of abatacept in healthy adults and adults with RA have been characterised previously and are summarised adequately in the current product information. Further evaluation of the PK of abatacept was not submitted with this application which was considered acceptable by the CHMP.

2.3.3. Pharmacodynamics

Anti-CCP and Rheumatoid Factor

All but 2 subjects in study IM101226 were positive for anti-CCP at baseline, consistent with protocol requirements. While most subjects in all 3 treatment groups remained positive for anti-CCP at the end of the Treatment Period (TP Day 365), the percentage who became negative for anti-CCP was higher for the abatacept + MTX group (8/98, 8%) than for the MTX monotherapy (1/94, 1%) or abatacept monotherapy (1/85, 1%) groups. At the end of the Withdrawal Period (WP Day 365), all subjects who were positive for anti-CCP remained positive and the subject in the abatacept monotherapy group who was negative for

anti-CCP remained negative. The majority of the subjects in all 3 treatment groups remained positive for anti-CCP at the end of the Re-exposure Period (RP Day 169); a higher percentage of subjects in the abatacept + MTX group (5/46, 11%) were negative for anti-CCP compared with the abatacept monotherapy (0/41, 0%) and MTX monotherapy (1/37, 2.7%) groups.

Similarly, the percentage of subjects who were RF positive at baseline but RF negative at TP Day 365 was higher for the abatacept + MTX group (16/95, 17%) than for the MTX monotherapy (10/93, 11%) or abatacept monotherapy (6/83, 7%) groups. None of the 5 subjects in the abatacept + MTX group who were RF negative at baseline seroconverted during the Treatment Period, compared to 1 of 6 subjects in the MTX monotherapy group and 1 of 3 subjects in the abatacept monotherapy group. At the end of the Withdrawal Period (WP Day 365), the majority (≥90% in each group) of the subjects were still RF positive. At the end of the Re-exposure Period, the percentage of subjects who were RF positive at baseline but RF negative at RP Day 169 was higher for the abatacept + MTX group (4/46, 9%) than for the MTX monotherapy (2/37, 5%) or abatacept monotherapy (2/39, 5%) groups.

Changes from Baseline in hsCRP Levels

Mean reductions were seen in hsCRP levels in all groups as early as TP Day 29 (first assessment time point), and in general, mean reductions during the Treatment Period were similar for the abatacept + MTX and abatacept monotherapy groups and smaller for the MTX monotherapy group. At TP Day 365, the mean (SE) reductions in hsCRP for the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups were -12.73 (2.24), -11.63 (2.49), and -8.01 (2.27) mg/L, respectively. Mean hsCRP values rose following discontinuation of study drug during the Withdrawal Period; at WP Day 365, the mean reductions in hsCRP for the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups were -4.19 (5.79), -2.57 (6.50), and -10.01 (5.32) mg/L, respectively. Following retreatment with abatacept during the Re-exposure Period, mean hsCRP values returned to values seen during the Treatment Period; at RP Day 169, the mean reductions in hsCRP for the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups were -12.77 (3.02), -13.05 (3.06), and -13.85 (3.40) mg/L, respectively.

2.3.4. Discussion on clinical pharmacology

No new pharmacology data was submitted with this application with the exception of some limited pharmacodynamic data from the pivotal study IM101226. These include anti-CCP, Rheumatoid Factor Status (cross-classification), and hsCRP Levels. Data on immunogenicity were also collected but these are discussed in the Clinical Safety Section of this report.

During treatment period, the percentage that became negative for anti-CCP or RF was higher for the combination (abatacept + MTX) group than for the MTX monotherapy or abatacept monotherapy groups. However, the classification of the majority of patients remained unchanged. None of the 5 subjects in the combination group who were RF negative at baseline seroconverted during the treatment period (in contrary with monotherapy groups, in which respectively 1-1 subjects have been converted). At the end of the withdrawal period the anti-CCP status of the patients was not changed, and in the end of the withdrawal period more than 90% of the subjects were still RF positive.

Reductions were seen in hsCRP levels in all groups as early as day 29, and in general, mean reductions during the treatment period were similar for the abatacept + MTX and abatacept monotherapy groups but smaller for the MTX monotherapy group. These changes reversed upon discontinuation and returned to similar decreased levels after retreatment with abatacept.

2.3.5. Conclusions on clinical pharmacology

The scope of the clinical pharmacology program of Study IM101226 was limited and did not provide any information that would warrant an update to the product information.

2.4. Clinical efficacy

2.4.1. Dose response studies

Not applicable.

2.4.2. Main study

Title of Study

AVERT (Study IM101226): A Phase 3b, randomized, active controlled trial to evaluate the efficacy and safety of abatacept SC in combination with methotrexate in inducing clinical remission compared to methotrexate monotherapy in adults with very early RA.

Methods

Study participants

Key inclusion criteria

• Men and women (not nursing or pregnant) at least 18 years of age at the time of informed consent

• A DAS28-CRP score of 3.2 or higher at screening visit

• Presence of active clinical synovitis of at least 2 joints, 1 of which must have been a small joint, for a minimum of 8 weeks at screening visit. Distal interphalangeal joints did not count toward this requirement

• Onset of persistent symptoms for ≤ 2 years prior to screening

• Positive for anti-CCP2

• Methotrexate naive or who had minimum exposure to MTX (defined as no more than 10 mg/week for ≤ 4 weeks and no MTX dose for 1 month prior to screening visit)

• Biologic naive, including no treatment with an investigational biologic prior to screening

• Withdrawn from any treatment with chloroquine, hydroxychloroquine, and/or sulfasalazine (wash-out) for a minimum of 28 days prior to randomization

• If receiving oral corticosteroids, on a stable low dose (≤ 10 mg/day prednisone equivalent) for at least 4 weeks

• Able to receive an MRI

Key Exclusion Criteria

Key exclusion criteria included the following:

• Met diagnostic criteria for other rheumatic disease (e.g., lupus erythematosus)

• Treatment with an IV, intramuscular [IM], or intra-articular [IA] corticosteroid within 4 weeks prior to randomization

• Scheduled for or anticipating joint replacement surgery

• Currently receiving treatment with molecular biologic therapies (including, but not limited to, tumor necrosis factor-α 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 (no washout required for immunoadsorption columns).

• 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, specifically:

– a history of cancer within the last 5 years (other than non-melanoma skin cell cancers cured by local resection)

– evidence of current malignancy or signs of possible malignancy detected by screening procedures for which the workup to exclude malignancy was not completed or malignancy cannot be excluded

– female subjects who had a breast cancer imaging screening study that was suspicious for malignancy and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations

– subjects with non-melanoma skin cell cancers present at or before screening which had been entirely removed prior to enrollment, or those with cancer in situ present at or before screening that have been treated with definitive surgical intervention prior to enrollment were eligible for enrollment.

• At risk for tuberculosis (TB), as indicated by current clinical, radiographic, or laboratory evidence of active TB; a history of active TB within the last 3 years (even if it was treated); a history of active TB longer than 3 years ago without documentation that prior anti-TB treatment was appropriate in duration and type; or latent TB that was not successfully treated

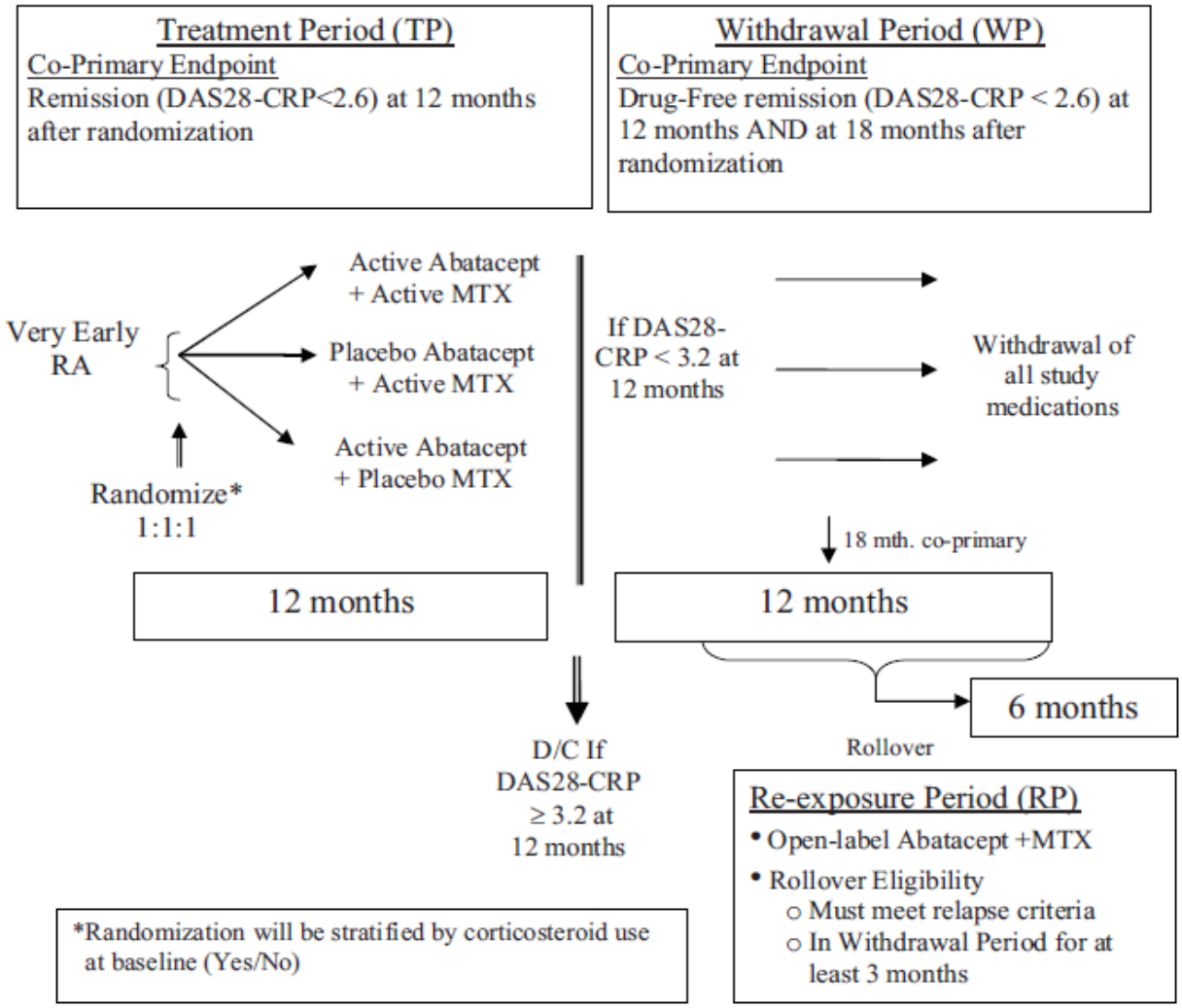
• Any serious bacterial infection within the last 3 months not treated or resolved within antibiotics, or any chronic or recurrent bacterial infection

• 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 enrollment.

Treatments

The study design is presented in Figure 1.

Figure 1: Schematic design of Study IM101226


Treatment Period (TP)
Co-Primary Endpoint
Remission (DAS28-CRP<2.6) at 12 months after randomization
Withdrawal Period (WP)
Co-Primary Endpoint
Drug-Free remission (DAS28-CRP < 2.6) at 12 months AND at 18 months after randomization
Very Early RA
Active Abatacept + Active MTX
Placebo Abatacept + Active MTX
Active Abatacept + Placebo MTX
Randomize* 1:1:1
12 months
If DAS28-CRP < 3.2 at 12 months
Withdrawal of all study medications
18 mth. co-primary
12 months
6 months
Rollover
D/C If DAS28-CRP ≥ 3.2 at 12 months
Re-exposure Period (RP)
• Open-label Abatacept +MTX
• Rollover Eligibility
o Must meet relapse criteria
o In Withdrawal Period for at least 3 months
*Randomization will be stratified by corticosteroid use at baseline (Yes/No)

The study comprised three periods: the treatment period (12 months), the withdrawal period (3-6 months; 12 months for those not entering the RE-exposure period) and the re-exposure period (6months). Subjects received 1 of 3 treatments (abatacept 125 mg SC + MTX tablets; abatacept 125 mg SC + placebo MTX tablets; or placebo SC + MTX tablets) on a weekly basis according to the dosing schedule outlined below during the Treatment Period, beginning on Day 1 and continuing through Day 358 (Months 1 to 12).

Treatment period

Test product, dose, mode of administration, duration of treatment:

Abatacept for injection was supplied as pre-filled, ready-to-use, glass syringes each containing 125 mg of abatacept per syringe (125 mg/mL). Abatacept was administered SC by the subject on Day 1 and weekly thereafter during the Treatment Period.

Reference therapy, Dose and mode of administration, duration of treatment

Methotrexate was supplied as 2.5 mg tablets for weekly oral administration during the Treatment Period, and was titrated over a period of 6 to 8 weeks based on tolerability: Week 1, 7.5 mg; Week 2, 10 mg; Week 3, 12.5 mg; Week 4, 15 mg; Week 5, 17.5 mg; Week 6, 20 mg. The maximum tolerable dose of MTX achieved at Week 6 was maintained throughout the remainder of the Treatment Period. Down titration was permitted only for tolerability reasons to a minimum of 10 mg/week. Placebo matching abatacept was supplied as pre-filled, ready-to-use glass syringes for weekly SC administration during the Treatment Period. Placebo matching MTX was supplied as similarly-appearing tablets for oral weekly administration during the Treatment Period.

Prior and Concomitant medication

The use of any approved or investigational biologic therapy for RA was prohibited. In addition, subjects were not to have received > 4 weeks of prior treatment with MTX at a dose of ≤ 10 mg/week, and were not to have received any MTX dose for at least 1 month prior to the screening visit. Any prior treatment with chloroquine, hydroxychloroquine, and/or sulfasalazine was to have been discontinued at least 28 days prior to randomization. Any prior use of azathioprine, gold, leflunomide, mycophenylate mofetil, cyclosporine, other calcineurin inhibitors, D-penicillamine, or immunosorption columns must have been discontinued at least 3 months prior to the screening visit. Subjects who were enrolled on oral corticosteroids were required to be on a stable, low dose (i.e., ≤ 10 mg prednisone equivalent) for at least 4 weeks prior to randomization, and prior use of an injectable corticosteroid was to be given at least 4 weeks prior to randomization. In addition, up to two of the following high dose corticosteroid courses are permitted during the treatment period at the discretion of the investigator: a short (maximum 2 week) oral course of high dose corticosteroids (according to local standard of care); a single IM or IV dose of a corticosteroid; a single intra-articular injection of corticosteroids.
The administration of a live virus vaccine was prohibited for a minimum of 3 months prior to the first dose of study drug, during the study, and for 3 months after the last dose of study drug.
The use of non-steroidal anti-inflammatory drugs (NSAIDS), including aspirin, was permitted during the Treatment Period, except within 12 hours prior to a joint count assessment, provided the dose was stable. The only acceptable reason for a decrease in NSAID dosage was toxicity or intolerance.

Subjects were permitted to take the following analgesics during the study for the treatment of pain not adequately controlled by baseline and study medications, except for the 12 hours prior to a joint count assessment: acetaminophen (paracetamol), narcotic analgesics or combination products containing acetaminophen and a narcotic analgesic, or tramadol.

Withdrawal Period

No treatment with abatacept or placebo SC was administered during the Withdrawal Period. The dose of MTX or placebo tablets at the end of the Treatment Period was tapered downward to a dose of 0 mg over the first month of the Withdrawal Period at a rate of decrease of at least 1 tablet/week. Corticosteroids were also tapered.

All subjects who entered the Re-exposure Period received open-label abatacept 125 mg SC and oral MTX tablets once weekly. Subjects were permitted to adjust the restricted medications at the discretion of the investigator based upon the subject's clinical status.

In addition, one of the following therapies could be added at the investigators discretion and according to the manufacturer's recommendations: sulfasalazine, chloroquine, or hydroxychloroquine.

Any concomitant medication listed in the prescribing label of the subject's background therapy was evaluated by the Investigator for continued administration during the subject's participation in this study.

Prohibited medication was the same as for the Treatment Period except subjects receiving treatment with oral corticosteroids who should have them tapered during the first month.

In addition, one of the following high dose corticosteroid courses was permitted during the withdrawal period at the discretion of the investigator: A short (maximum 2 week) oral course of high dose corticosteroids (according to local standard of care); A single IM or IV dose of a corticosteroid; A single intra-articular injection of corticosteroids.

These allowances did not apply within 28 days of the WP 169 visit. A joint that received an intra-articular injection was counted as 'active' for the remainder of the study.

Re-exposure Period

Same as Treatment/Withdrawal Period except DMARDs were permitted.

Objectives

The 2 co-primary objectives were to compare the clinical efficacy of abatacept in combination with methotrexate (MTX) to MTX alone on the following:

• The proportion of randomized and treated subjects with Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) < 2.6 at Month 12

• The proportion of randomized and treated subjects with DAS28-CRP < 2.6 at both Month 12 and Month 18.

Secondary study objectives included:

• To assess physical function and health-related quality of life using Health Assessment Questionnaire (HAQ) and Short-Form 36 (SF-36) (version 2.0) in the abatacept/MTX combination, abatacept monotherapy, and MTX monotherapy arms

• To assess joint damage progression by magnetic resonance imaging (MRI) scoring at Months 6, 12, and 18 in the abatacept/MTX combination, abatacept monotherapy, and MTX monotherapy arms

• To assess safety and tolerability including immunogenicity in the abatacept/MTX combination, abatacept monotherapy, and MTX monotherapy arms

Outcomes/endpoints

The pre-specified co-primary efficacy endpoints were:

• The proportion of randomized and treated subjects in the abatacept + MTX and MTX monotherapy groups in DAS28-CRP remission (defined as DAS28-CRP score < 2.6) at TP Day 365 (Month 12 after randomization)

• Proportion of randomized and treated subjects in the abatacept + MTX and MTX monotherapy groups in DAS28-CRP Remission at both TP Day 365 and WP Day 169 (Months 12 and 18, after randomization).

Pre-specified secondary efficacy endpoints (selected):

• Proportion of subjects in DAS28-CRP Remission at WP Day 169 (Month 18) who were in DAS28-CRP LDAS (DAS28-CRP < 3.2) at TP Day 365 (Month 12 after randomization)

• Proportion of subjects achieving a HAQ response at Day 169 (Month 6 after randomization), as measured by a reduction of at least 0.3 units from baseline in HAQ Disability Index (HAQ-DI)

• Adjusted mean change from baseline over time in DAS28-CRP, adjusted for baseline value and corticosteroid use stratification

• Proportion of subjects achieving SDAI-defined remission criteria of ≤ 3.3 at TP Day 365 (Month 12 after randomization) and at WP Day 169 (Month 18 after randomization)

• Proportion of subjects with a HAQ response (defined as a reduction from baseline in the HAQ-DI of at least 0.3 points) over time

• Adjusted mean change from baseline over time in HAQ-DI

• Adjusted mean change from baseline in erosion, synovitis and osteitis scores based on MRI scoring at TP Day 169, TP Day 365, WP Day 169, and WP Day 365 (Study Months 6, 12, and 18 after randomisation).

Sample size

A total of 116 subjects per treatment group (approximately 348 total subjects) was assumed to yield 90% power to detect a difference of 22% in the first co-primary efficacy endpoint, the proportion of subjects in remission at Month 12 in the Treatment Period between the abatacept + MTX and MTX monotherapy groups. This power estimate assumed a 2-sided alpha level of 5%, and that 60% of subjects in the abatacept + MTX group would be in DAS28-CRP remission at Month 12 (TP Day 365) compared with 38% of the subjects in the MTX monotherapy group**.** It was further assumed that 48% of subjects in the abatacept monotherapy group would be in DAS28-CRP remission at Month 12 (TP Day 365), yielding an expected treatment difference from MTX of 10% in favor of abatacept monotherapy. A total of 116 subjects randomized to the abatacept monotherapy group would yield a half-length of the 95% confidence interval (CI) around that 10% treatment difference of 13.5%.

Conditional on the first co-primary efficacy analysis being statistically significant, a sample size of 116 subjects per treatment group would also provide 98% power for the second co-primary efficacy analysis - comparison of the proportion of subjects in DAS28-CRP remission at both Month 12 [TP Day 365] and Month 18 [WP Day 169]) between the abatacept + MTX group and the MTX monotherapy group for intent-to treat (ITT) population.

Randomisation

At the time of enrolment, each subject was assigned a unique sequential subject number for identification throughout the study via the Central Randomisation System (interactive voice randomization system [IVRS]). Sites were to contact the Central Randomization System when subjects provided informed consent. Randomization schedules were generated and retained by the Randomization Group within Drug Supply Management of BMS until study un-blinding. Each subject who was qualified for randomization was assigned

a unique randomization number via IVRS in the order in which the subjects qualified for treatment. Randomization was stratified by corticosteroid use at the time of the screening visit. After completion of all screening evaluations, all eligible subjects were randomized 1:1:1 to abatacept SC + MTX, abatacept SC + placebo tablets, or MTX + placebo SC based on corticosteroid use.

Blinding (masking)

The subjects and clinical investigational staff were blinded to the randomized treatment assignment throughout the Treatment Period.

Statistical methods

The populations for analyses were defined by study periods.

Treatment Period

Unless otherwise specified, analyses of efficacy and outcome endpoints for the Treatment Period were performed using the Intention to Treat (ITT) analysis population. Analyses of safety and exposure data for the Treatment Period were based on the As-treated analysis population.

Withdrawal and Re-exposure Periods

Unless otherwise specified, analyses of efficacy endpoints involving time points during the Withdrawal and Re-exposure Periods were reported for the ITT analysis population. For the efficacy analyses, subjects were analyzed according to the treatment to which they were randomized in the Treatment Period. Safety analyses (AEs, clinical laboratory data, and vital signs) for the Withdrawal and Re-exposure Periods were performed using the All Treated Subjects Entering the Withdrawal Period analysis population or the All Treated Subjects Entering the Re-exposure Period analysis population, respectively, that included all subjects who continued into the Withdrawal or Re-exposure Periods.

Efficacy Analyses

Except for the co-primary efficacy analyses, no formal statistical testing was performed for any secondary efficacy endpoints.

All construction of CIs for a response rate within a treatment group for a specific time point were based on normal approximation, provided there were at least 5 events in each treatment group; otherwise, the exact method was used. The 95% CI for treatment difference in response rate was constructed using the continuity correction. All tests and CIs were 2-sided.

Unless otherwise specified, adjusted mean changes from baseline were analyzed using a longitudinal repeated measures analysis with direct likelihood estimation on the change form baseline, using an observed cases dataset. For each scale (DAS28-CRP, SDAI, etc.), the model included fixed categorical effects of treatment, months, prior corticosteroid use (Yes/No),months-by-treatment interaction as well as the continuous fixed covariate of baseline value. An unstructured covariance matrix was used to represent the correlation of the repeated measures within each subject.

Co-primary Efficacy Analyses

Statistical testing of the 2 co-primary efficacy endpoints was conducted in a hierarchical fashion to maintain the overall Type I error rate at 5%. Specifically, formal treatment comparison of the proportion of subjects in DAS28-CRP remission at both Month 12 and Month 18 (second co-primary endpoint) was performed only if the treatment comparison of the proportion of subjects in DAS28-CRP remission at Month 12 (first co-primary endpoint) was statistically significant.

Analysis of the first co-primary endpoint involved a comparison of the abatacept + MTX group and the MTX monotherapy group using an adjusted logistic regression test that included treatment, baseline DAS28-CRP value, and the stratification factor of corticosteroid use at baseline (Yes/No) as explanatory variables in the model, and was tested at a 5% significance level. In this analysis, all subjects who prematurely discontinued the study for any reason were considered not to have achieved remission. The odds ratio estimate, corresponding 95% CI, and p-value were provided from the logistic regression for abatacept + MTX vs. MTX monotherapy.

Analysis of the second co-primary endpoint used a similar adjusted logistic regression test. All subjects who prematurely discontinued the study for any reason, or who were not eligible to enter the Withdrawal Period, or who entered the Re-exposure Period were considered not to have achieved remission for all time points after discontinuation date or entry into the Re-exposure Period.

As a sensitivity analysis for both co-primary efficacy analyses, a stratified Cochran-Mantel-Haenszel (CMH) Chi-square test, stratified by corticosteroid use at baseline (Yes/No), was performed at a 5% significance level. The relative risk and the Chi-square p-value, along with its 95% CI were provided, together with the absolute treatment difference and corresponding 95% CI.

Secondary Efficacy Analyses

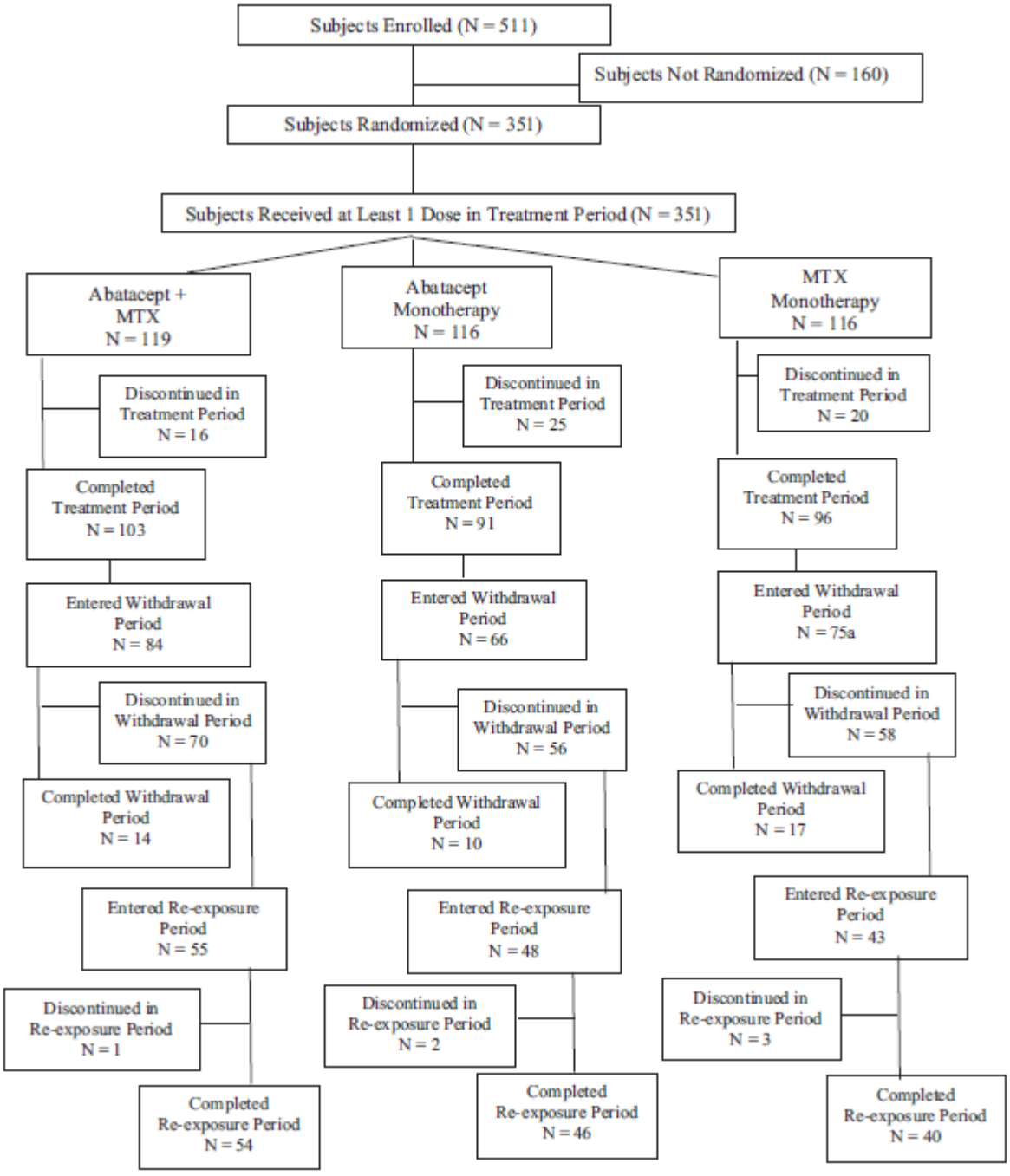
For all secondary efficacy analyses examining remission, subjects who prematurely discontinued the study for any reason, or who were not eligible to enter the Withdrawal Period, or who entered the Re-exposure Period were considered not to have achieved remission for all time points after discontinuation date or entry into the Re-exposure Period.

With respect to analyses of MRI data, in the event that there were > 20% of joints with a missing score for a parameter (erosion, osteitis, and synovitis), the MRI score of each parameter was considered missing. If there were ≤ 20% of joints with a missing score for a parameter, the MRI score for that parameter from the missing joints was carried forward from the previous MRI assessment, or carried backward from the next MRI assessment if missing score occurred at baseline.

Results

Participant flow

Figure 2. Patient Disposition in Study IM101226 - All Enrolled Subjects



Recruitment

The study was conducted in seventy-two sites worldwide, in the United States - 17, Mexico - 9, Australia, Germany, Poland, and South Africa - 6 each, Sweden - 5, France - 4, Belgium - 3, Finland - 2, and Denmark and Italy - 1 each.

Study Initiation Date: 10-Dec-2010 Clinical Phase 3b Study Completion Date: 27-Oct-2014

Conduct of the study

Protocol Deviations

Significant Deviations

The most common types of significant protocol deviations were related to inclusion/exclusion criteria deviations (84 subjects) and incorrect dosing or study drug assignment (83 subjects). A total of 61 subjects did not meet the inclusion criteria for active clinical synovitis at least 8 weeks before the screening visit. The most commonly reported dosing deviation involved a failure to follow MTX dosing recommendations or the titration schedule specified in the protocol (77 subjects).

Changes in the Conduct of the Study

There was 1 amendment to the protocol (dated 17-May-2011). The major changes to the protocol included the following:

• update of the time frame for stable oral corticosteroid use as well as allowed routes of administration

• inclusion of additional secondary and exploratory objectives

•addition of wash-out requirements for subjects taking chloroquine, hydroxychloroquine, and sulfasalazine prior to randomization

• addition of prohibited use of IA, IM, IV, or oral corticosteroids within 28 days of WP Day 169

• additional text to clarify MTX titration during the Treatment Period

• definition of SDAI and CDAI and inclusion of these 2 new analyses as secondary and exploratory objectives

Changes to the Planned Analyses

Changes Prior to Database Un-blinding

Prior to database un-blinding, the primary analysis of the primary efficacy variable was changed to an adjusted logistic regression, and the protocol-specified analysis for this variable using the Chi-square test was specified as a sensitivity analysis. The change was implemented as the adjusted logistic regression allowed all subjects from all 3 treatment groups to be included in the analysis model. Prior to database un-blinding, the first secondary efficacy-related objective (i.e., abatacept monotherapy vs. MTX monotherapy) was raised in the ordering of secondary objective from the fourth position due to higher clinical relevance.

Changes After Database Un-blinding

After the database was un-blinded, the definition for determination of the SDAI was changed from an hsCRP unit of mg/L (as specified in the protocol and SAP) to mg/dL. Accordingly, all planned analyses for SDAI were repeated using the updated unit of measure for hsCRP. This change was implemented to allow comparison with other abatacept clinical studies that included SDAI as a study endpoint. Sensitivity analyses of efficacy and safety were conducted to assess the potential effect of missing or erroneous first or last dose dates.

Baseline data

Baseline / Demographic Characteristics

The 3 treatment groups were balanced with respect to demographic and baseline disease characteristics at entry into the Treatment Period (**Tables 1** and **2**).

Table 1. Baseline and Demographic Characteristics in Study IM101226 - ITT Population

	Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116
Age years, mean (SD)	46.4 (13.20)	45.4 (11.92)	49.1 (12.36)
Female, n (%)	95 (79.8)	89 (76.7)	89 (76.7)
Race, n (%)			
White	100 (84.0)	95 (81.9)	102 (87.9)
Asian	14 (11.8)	13 (11.2)	9 (7.8)
Black-African American	2 (1.7)	4 (3.4)	2 (1.7)
Other	3 (2.5)	4 (3.4)	3 (2.6)
Duration of RA Symptoms (years), mean (SD)	0.58 (0.50)	0.59 (0.52)	0.50 (0.49)
CRP (ng/mL), mean (SD)	18.110 (28.3760)	16.935 (23.9232)	17.344 (22.3991)
DAS28-CRP Score, mean (SD)	5.53 (1.25)	5.46 (1.15)	5.32 (1.33)
HAQ-DI Score, mean (SD)	1.45 (0.68)	1.42 (0.66)	1.38 (0.65)
RF Positive, n (%)	113 (95.0)	111 (95.7)	110 (94.8)
Tender Joint Count, mean (SD)	24.3 (15.74)	23.9 (14.47)	21.7 (14.00)
Swollen Joint Count, mean (SD)	16.5 (12.43)	17.2 (12.88)	15.7 (11.78)

Table 2. Baseline Disease Characteristics in Study IM101226-ITT Population

		Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116	Total N = 351
Duration of Synovitis (Months)	N	119	116	116	351
	MEAN	6.95	7.11	5.97	6.68
	SD	5.998	6.263	5.858	6.045
	MEDIAN	4.60	5.19	3.52	4.44
	MIN	0.0	0.0	0.0	0.0
	MAX	22.3	22.6	24.0	24.0
Duration of Synovitis	< 6 MONTHS	70 (58.8%)	71 (61.2%)	77 (66.4%)	218 (62.1%)
	>= 6 MONTHS	49 (41.2%)	45 (38.8%)	39 (33.6%)	133 (37.9%)
Baseline DAS28CRP	MISSING	4 (3.4%)	3 (2.6%)	1 (0.9%)	8 (2.3%)
	LDAS	1 (0.8%)	0	6 (5.2%)	7 (2.0%)
	MDAS	40 (33.6%)	45 (38.8%)	44 (37.9%)	129 (36.8%)
	HDAS	74 (62.2%)	68 (58.6%)	65 (56.0%)	207 (59.0%)
Screening DAS28CRP	MISSING	8 (6.7%)	5 (4.3%)	1 (0.9%)	14 (4.0%)
	LDAS	1 (0.8%)	1 (0.9%)	1 (0.9%)	3 (0.9%)
	MDAS	44 (37.0%)	49 (42.2%)	51 (44.0%)	144 (41.0%)
	HDAS	66 (55.5%)	61 (52.6%)	63 (54.3%)	190 (54.1%)
Age	< 65 YEARS	109 (91.6%)	109 (94.0%)	104 (89.7%)	322 (91.7%)
	65 - 74 YEARS	8 (6.7%)	6 (5.2%)	12 (10.3%)	26 (7.4%)
	75 - 84 YEARS	2 (1.7%)	1 (0.9%)	0	3 (0.9%)
	>= 85 YEARS	0	0	0	0

Baseline is Day 1 of the study. Treatment groups represent treatment received in the Treatment Period. LDAS is defined as DAS28-CRP < 3.2, MDAS is defined as 3.2 <= DAS28-CRP <= 5.1 and HDAS is defined as DAS28-CRP > 5.1

Majority of patients were positive for antibodies to citrullinated protein antigens (ACPA), with 90.8% of the patients in the abatacept+MTX group having high anti-cyclic citrullinated peptide-2 (CCP2) and similar percentages for the abatacept and MTX groups (90.5 and 93.1 respectively).

Previous treatments

Anti-rheumatic medication history was generally consistent across the 3 treatment groups. Prior to screening, most of the subjects who were subsequently randomized had received anti-rheumatic therapy. Only 6% had received prior treatment with MTX. Less than half of the subjects had received prior treatment with oral and/or injectable corticosteroids, with a mean oral dose of 8.4 mg.

There was little change in the percentage of subjects who received NSAIDs or corticosteroids during screening and at enrolment (79% and 32%, respectively) relative to the use of these drugs prior to screening. Two subjects assigned to the abatacept + MTX group were receiving a DMARD (hydroxychloroquine) during screening/enrolment. For both subjects, the DMARD was discontinued 1 day prior to the Day 1 visit. These were considered significant protocol deviations.

Concomitant medication

At Day 1, 32% of the randomized and treated subjects were receiving oral and/or injectable corticosteroids, and the use of these drugs was similar across the 3 treatment groups. Fewer subjects in the abatacept + MTX group received 1 or 2 courses of high-dose corticosteroid therapy during the Treatment Period compared with the other groups.

The most common concomitant medications (other than corticosteroids) used during the Treatment Period (at least 20% in any treatment group) were folic acid (98% in all 3 groups), acetaminophen (28% to 34% across groups), diclofenac (19% to 24%), and omeprazole (19% to 33%).

Numbers analysed

Efficacy and safety data from all subjects were analyzed according to the treatment group assignment in accordance with the randomization schedule.

The ITT and All Treated Subjects analysis populations for the Treatment Period were identical, and included 351 subjects (119 in the abatacept + MTX group, 116 in the abatacept monotherapy group, and 116 in the MTX monotherapy group). The All Treated Subjects Entering the Withdrawal Period analysis population included 225 subjects who had entered the Withdrawal Period (84 in the abatacept + MTX group, 66 in the abatacept monotherapy group, and 75 in the MTX monotherapy group).

The All Treated Subjects Entering the Re-exposure Period analysis population included 146 subjects who had entered the Re-exposure Period (55 in the abatacept + MTX group, 48 in the abatacept monotherapy group, and 43 in the MTX monotherapy group).

Outcomes and estimation

Co-Primary efficacy variables: Sustained Remission at Month 12 and at 12 and 18 months

Abatacept 125 mg/day SC in combination with MTX showed significantly higher rates of remission on treatment at Month 12 as well as significantly higher rates of sustained remission after withdrawal of all RA therapy compared with treatment with MTX alone (Month 12 and 18) (**Table 3**).

Table 3. Summary of Co-Primary Efficacy Endpoints: Proportion of Subjects with DAS28-CRP Remission at Month 12 and at Both at Months 12 and 18 in Study IM101226 – ITT Population

Efficacy Endpoint	Month 12 (Treatment Period)			Month 12 to 18 (Withdrawal Period)		
	Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116	Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116
DAS28-CRP < 2.6, n/m (%)	70/115 (60.9)	48/113 (42.5)	52/115 (45.2)	17/115 (14.8)	14/113 (12.4)	9/115 (7.8)
Odds ratio (95% CI) vs. MTX	2.01 (1.18, 3.43)	0.92 (0.55, 1.57)	N/A	2.51 (1.02, 6.18)	2.04 (0.81, 5.14)	N/A
P value	0.010	N/A	N/A	0.045	N/A	N/A

Odds ratio and p-values are based on an Adjusted Logistic Regression test, including treatment (3 groups), baseline DAS28-CRP values as well as the stratification factor (corticosteroid use at baseline). ITT = Intent-to-treat; n = Number of subjects with DAS28-CRP Remission at Month 12, m = Number of subjects in the analysis, MTX = methotrexate, N/A = not applicable.

Pre-specified Analyses Using CMH Chi-square Test

Results of the sensitivity analyses of the co-primary endpoints, using a CMH Chi-square test stratified by baseline corticosteroid use, were consistent with those of the primary analyses using the adjusted logistic regression model. The treatment difference in the proportion of subjects in DAS28-CRP remission at Month 12 was 15.65, and favored the abatacept + MTX group over the MTX monotherapy group. Similarly, there was a 7.37 difference in the proportion of subjects in DAS28-CRP remission at both Month 12 and Month 18 between the abatacept +MTX and MTX monotherapy groups (**Tables 4 and 5**).

Table 4. Proportion of subjects with DAS28-CRP Remission at month 12 in Study IM101226 (Stratified CMH)-ITT population

	Abatacept + MTX N = 119	MTX N = 116
n (%)	73 (61.3%)	53 (45.7%)
95% CI*	(52.60, 70.09)	(36.62, 54.75)
RELATIVE RISK (95% CI)	1.35 (1.06, 1.72)	N/A
TREATMENT DIFFERENCE IN RATE (95% CI)	15.65 (2.21, 29.10)	N/A
P-VALUE	0.015	N/A

Table 5. Proportion of subjects with DAS28-CRP Remission at both month 12 and month 18 in Study IM101226 (Stratified CMH)-ITT population

	Abatacept + MTX N = 119	MTX N = 116
n (%)	18 (15.1%)	9 (7.8%)
95% CI*	(8.69, 21.56)	(2.89, 12.63)
RELATIVE RISK (95% CI)	1.89 (0.89, 3.99)	N/A
TREATMENT DIFFERENCE IN RATE (95% CI)	7.37 (-1.55, 16.29)	N/A
P-VALUE	0.090	N/A

Post Hoc Analyses by disease activity at baseline

Post hoc analysis of the proportion of subjects with DAS28-CRP remission at Month 12 by baseline disease activity is shown in **Table 6**.

Table 6. Study IM101226 - Proportion of Subjects with DAS28-CRP Remission at Month 12 by Baseline Characteristic Factors - ITT Population

Subgroup			SC ABA+MTX N=119	SC ABA N=116	MTX N=116
Baseline DAS28-CRP	Missing	Number of subject n/m (%)	3/4 (75.0%)	2/3 (66.7%)	1/1 (100.0%)
		95% CI*	(19.41, 99.37)	(9.43, 99.16)	(2.50, 100.00)
		Est. of Diff. vs. MTX (95% CI)	-25.0 (-175, 125.2)	-33.3 (-198, 131.3)	N/A
	< 3.2	Number of subject n/m (%)	1/1 (100.0%)	0	3/6 (50.0%)
		95% CI*	(2.50, 100.00)	(0.00, 0.00)	(11.81, 88.19)
		Est. of Diff. vs. MTX (95% CI)	50.0 (-113, 213.1)	NE	N/A
	>= 3.2 and <=5.1	Number of subject n/m (%)	27/40 (67.5%)	22/45 (48.9%)	22/44 (50.0%)
		95% CI*	(52.99, 82.01)	(34.28, 63.49)	(35.23, 64.77)
		Est. of Diff. vs. MTX (95% CI)	17.5 (-6.0, 41.0)	-1.1 (-24.1, 21.9)	N/A
	> 5.1	Number of subject n/m (%)	42/74 (56.8%)	26/68 (38.2%)	27/65 (41.5%)
		95% CI*	(45.47, 68.04)	(26.68, 49.79)	(29.56, 53.52)
		Est. of Diff. vs. MTX (95% CI)	15.3 (-2.8, 33.4)	-3.3 (-21.4, 14.8)	N/A

*DAS28-CRP Remission is defined as DAS28-CRP < 2.6. * Normal approximation is used if the number of subjects with DAS28-CRP Remission in subgroup for all treatment arms is at least 5. Otherwise an exact method is used. n = Number of subjects with measure/event of interest, m = Number of subjects in the analysis. Imputation rule: missing DAS28-CRP Remission not due to premature discontinuation and not at Treatment Period (TP) Day 1 or Withdrawal Period (WP) Day 169 is imputed as DAS28-CRP Remission if missing value between 2 observed DAS28-CRP Remissions.*

Post Hoc Analyses of Missing First Dose Date

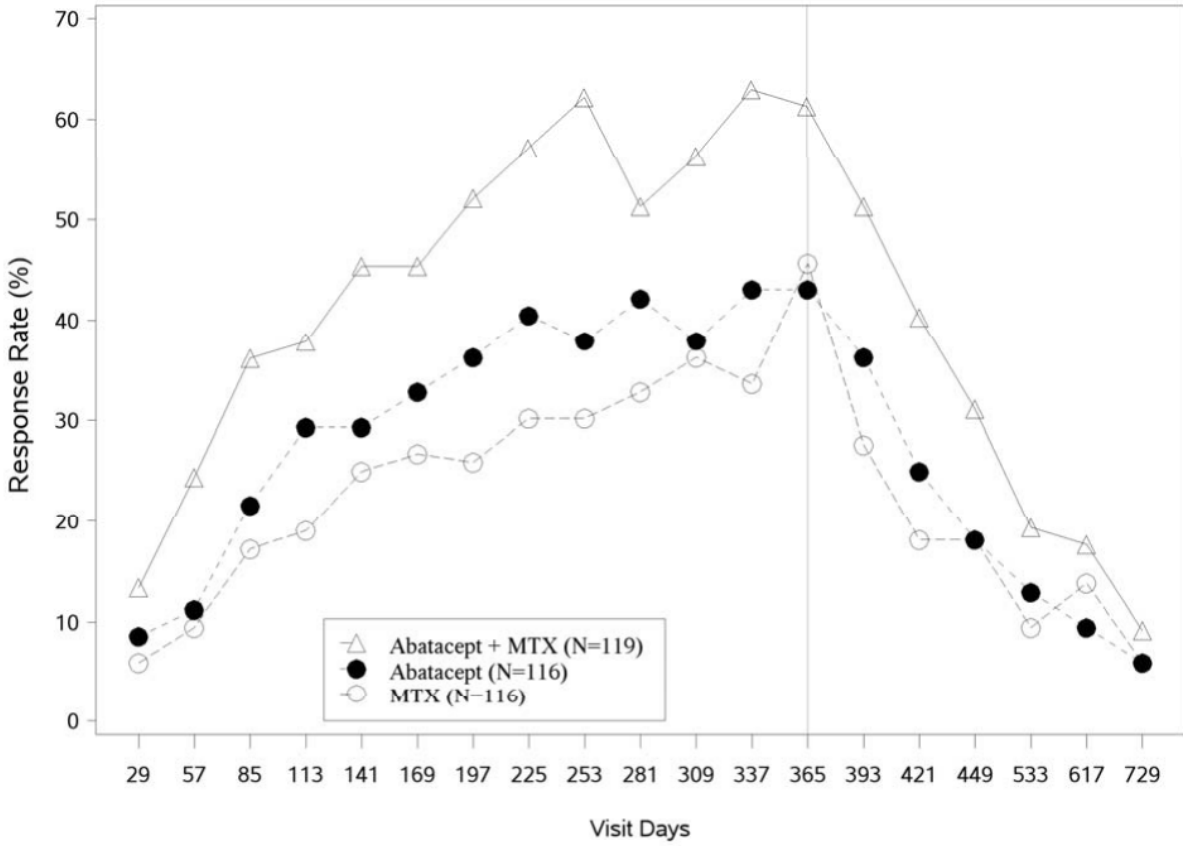
To account for the subjects with missing first dose dates, a sensitivity analysis was conducted in which the IVRS randomization date was used as the first dose date for all subjects. Results of this sensitivity analysis were consistent with the primary analysis; 69 of 114 (60.5%) subjects in the abatacept + MTX group and 52 of 114 (45.6%) subjects in the MTX monotherapy group met the criteria for DAS28-CRP remission (p = 0.014).

Results of secondary endpoints (selected)

DAS28-CRP Remission Rates Over Time in the Treatment and Withdrawal Periods

The proportion of the ITT analysis population who achieved DAS28-CRP remission at each scheduled assessment during the Treatment Period and Withdrawal Period is plotted by treatment group in **Figure 3**.

Figure 3. Proportion of Subjects with DAS28-CRP Remission Over Time in Study IM101226 – ITT Population



Day 365 line indicates end of treatment period

Table 7 presents the adjusted hazard ratio of having a relapse (or flare) during the 12-month Withdrawal Period (WP) between the abatacept + MTX group and the MTX monotherapy group. The adjusted hazard ratio and p-values were estimated based on a COX proportional Hazard model that included treatment (3 arms), baseline DAS28-CRP value, and the stratification factor (corticosteroid use at baseline).

Table 7. Relapse (flare) rate after withdrawal of all study medications in Study IM101226- All subjects who entered the withdrawal period

Endpoint	Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116
Relapse Rate (%)	57/83 (0.69)	48/66 (0.72)	44/75 (0.58)
Hazard Ratio (95% CI) vs MTX	1.094 (0.731,1.637)	1.123 (0.734,1.716)	NA
p-value	0.6626	0.5934	NA

HAQ-DI (physical function) at 12 months and 6 months after WP

The proportion of subjects with a clinically meaningful improvement (response) in physical function (change from baseline in HAQ DI score of ≥ 0.3) was greater for the abatacept + MTX group than for the MTX monotherapy group both at the end of the Treatment Period (67.2% vs 44%; treatment difference of 23.26, 95% CI = [10.05, 36.47]) and 6 months after withdrawal of all study medication (22.7% vs 10.3%; treatment difference of 12.3 [95% CI = 2.2, 22.5]).

The proportion of subjects with a HAQ DI response in the abatacept monotherapy group at the end of the Treatment Period and 6 months into the Withdrawal Period was 52.6% and 16.43%, respectively.

At Treatment Period Day 365 and Withdrawal Period Day 169 (Months 12 and 18 of study, respectively), the adjusted mean changes from baseline in the HAQ-DI score were -0.87 and -0.52, respectively, for the abatacept + MTX group; -0.73 and -0.49, respectively, for the abatacept monotherapy group; and -0.72 and -0.33, respectively, for the MTX monotherapy group.

SDAI (corrected) at 12 months

At Month 12 (Treatment Period Day 365), 50 subjects (42%) in the abatacept + MTX group and 34 subjects (29%) in the abatacept monotherapy group had achieved SDAI (corrected) remission compared with 29 subjects (25%) in the MTX monotherapy group; the estimated treatment differences were 17.02 (95% CI: 4.30, 29.73) and 4.31 (95% CI: -7.98, 16.61), respectively (abatacept + MTX or abatacept - MTX).

Upon discontinuation of study treatment, SDAI remission rates declined in all treatment groups, and were small and similar for all 3 treatment groups (8, 5, and 5 subjects, respectively, in the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups by Withdrawal Period Day 169 (Month 18) (7% to 12%).

Inhibition of progression of structural damage up to 12 months and after 6 months of Withdrawal

Treatment with abatacept + MTX was associated with a reduced progression in structural damage, as reflected by mean post baseline MRI erosion score, and improvements in MRI osteitis and synovitis scores at Month 12 (Treatment Period Day 365) and at Moth 18 (Withdrawal Period Day 169) (**Table 8**).

Table 8. Adjusted mean change from baseline over time in MRI scores in Study IM101226-ITT population

	Study Day		Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116
OSTEITIS	TP DAY 169	n	93	94	89
		BASELINE MEAN (SD)	4.51 (7.33)	4.22 (6.44)	3.99 (7.25)
		POST-BASELINE MEAN (SD)	2.27 (5.04)	3.04 (5.05)	3.28 (6.63)
		ADJUSTED MEAN CHANGE FROM BASELINE* (SE)	-2.03 (0.47)	-1.13 (0.47)	-0.73 (0.48)
		95% CI	(-2.96, -1.10)	(-2.05, -0.20)	(-1.67, 0.22)
		ADJUSTED MEAN DIFFERENCE VS. MTX* (95% CI)	-1.30 (-2.60, -0.01)	-0.40 (-1.69, 0.89)	N/A
	TP DAY 365	n	83	74	78
		BASELINE MEAN (SD)	4.41 (6.88)	4.34 (6.70)	3.43 (6.41)
		POST-BASELINE MEAN (SD)	1.70 (4.46)	2.55 (4.51)	2.81 (5.14)
		ADJUSTED MEAN CHANGE FROM BASELINE* (SE)	-2.32 (0.46)	-1.30 (0.46)	-0.90 (0.46)
		95% CI	(-3.22, -1.43)	(-2.21, -0.39)	(-1.81, 0.02)
		ADJUSTED MEAN DIFFERENCE VS. MTX* (95% CI)	-1.43 (-2.68, -0.18)	-0.40 (-1.66, 0.86)	N/A
	WP DAY 169	n	31	30	25
		BASELINE MEAN (SD)	3.55 (4.99)	6.00 (8.66)	3.00 (5.19)
		POST-BASELINE MEAN (SD)	1.87 (6.85)	5.07 (7.79)	2.76 (5.97)
		ADJUSTED MEAN CHANGE FROM BASELINE* (SE)	-1.94 (0.88)	0.98 (0.89)	-0.33 (0.96)
		95% CI	(-3.68, -0.20)	(-0.79, 2.74)	(-2.24, 1.58)
		ADJUSTED MEAN DIFFERENCE VS. MTX* (95% CI)	-1.61 (-4.18, 0.95)	1.31 (-1.28, 3.89)	N/A

EROSION	TP DAY 169	n	93	94	89
		BASELINE MEAN (SD)	7.15 (7.56)	5.11 (4.66)	6.54 (7.67)
		POST-BASELINE MEAN (SD)	7.53 (8.08)	6.30 (5.50)	7.67 (8.39)
		ADJUSTED MEAN CHANGE FROM BASELINE* (SE)	0.26 (0.28)	1.15 (0.28)	1.15 (0.28)
		95% CI	(-0.28, 0.81)	(0.61, 1.69)	(0.60, 1.70)
		ADJUSTED MEAN DIFFERENCE VS. MTX* (95% CI)	-0.89 (-1.65, -0.14)	-0.00 (-0.76, 0.76)	N/A
	TP DAY 365	n	83	74	78
		BASELINE MEAN (SD)	7.20 (7.00)	5.09 (4.70)	6.34 (7.77)
		POST-BASELINE MEAN (SD)	7.57 (7.50)	6.43 (6.10)	7.82 (8.70)
		ADJUSTED MEAN CHANGE FROM BASELINE* (SE)	0.34 (0.35)	1.57 (0.36)	1.56 (0.36)
		95% CI	(-0.35, 1.04)	(0.87, 2.27)	(0.86, 2.27)
		ADJUSTED MEAN DIFFERENCE VS. MTX* (95% CI)	-1.22 (-2.20, -0.25)	0.01 (-0.97, 0.99)	N/A
	WP DAY 169	n	31	30	25
		BASELINE MEAN (SD)	5.35 (5.11)	5.75 (5.03)	5.04 (5.17)
		POST-BASELINE MEAN (SD)	6.34 (6.72)	7.23 (6.48)	6.68 (7.28)
		ADJUSTED MEAN CHANGE FROM BASELINE* (SE)	0.20 (0.47)	2.16 (0.48)	1.89 (0.50)
		95% CI	(-0.74, 1.14)	(1.21, 3.11)	(0.90, 2.87)
		ADJUSTED MEAN DIFFERENCE VS. MTX* (95% CI)	-1.69 (-3.04, -0.33)	0.28 (-1.08, 1.64)	N/A
SYNOVITIS	TP DAY 169	n	93	94	89
		BASELINE MEAN (SD)	5.52 (4.24)	5.36 (4.06)	5.85 (4.51)
		POST-BASELINE MEAN (SD)	3.75 (2.90)	4.50 (3.34)	4.98 (4.01)
		ADJUSTED MEAN CHANGE FROM BASELINE* (SE)	-1.82 (0.21)	-0.93 (0.21)	-0.78 (0.21)
		95% CI	(-2.23, -1.40)	(-1.34, -0.52)	(-1.20, -0.35)
		ADJUSTED MEAN DIFFERENCE VS. MTX* (95% CI)	-1.04 (-1.62, -0.46)	-0.15 (-0.73, 0.42)	N/A
	TP DAY 365	n	83	74	78
		BASELINE MEAN (SD)	5.62 (4.18)	5.30 (3.84)	5.66 (4.24)
		POST-BASELINE MEAN (SD)	3.19 (2.32)	3.89 (3.07)	4.70 (3.64)
		ADJUSTED MEAN CHANGE FROM BASELINE* (SE)	-2.38 (0.29)	-1.36 (0.30)	-0.77 (0.30)
		95% CI	(-2.96, -1.80)	(-1.96, -0.77)	(-1.37, -0.18)
		ADJUSTED MEAN DIFFERENCE VS. MTX* (95% CI)	-1.60 (-2.42, -0.78)	-0.59 (-1.43, 0.24)	N/A
	WP DAY 169	n	31	30	25
		BASELINE MEAN (SD)	5.18 (3.82)	5.53 (3.56)	5.42 (4.87)
		POST-BASELINE MEAN (SD)	3.71 (3.22)	4.38 (3.70)	4.20 (4.31)
		ADJUSTED MEAN CHANGE FROM BASELINE* (SE)	-1.71 (0.45)	-0.95 (0.45)	-0.71 (0.49)
		95% CI	(-2.59, -0.82)	(-1.85, -0.05)	(-1.68, 0.27)
		ADJUSTED MEAN DIFFERENCE VS. MTX* (95% CI)	-1.00 (-2.31, 0.31)	-0.25 (-1.57, 1.07)	N/A

n is the number of subjects with both post-baseline and baseline measurements.
TP = Treatment Period, WP = Withdrawal Period, N/A = not applicable.
* Longitudinal Repeated Measures Model: Change from Baseline = Baseline Score, Treatment, Month, Prior corticosteroid use (Yes/No), Month*Treatment.
Unstructured covariance matrix for the correlation of the repeated measures within subject.

Proportion of Subjects Achieving DAS28-CRP remission and MRI non-progression

At both time points during the Treatment Period (6 and 12 months), a higher percentage of subjects in the abatacept + MTX group achieved DAS28-CRP remission together with MRI non-progression in erosion, osteitis, and synovitis (TP Day 365 values of 42.9%, 48.7%, and 49.6%, respectively) compared with the MTX monotherapy group (TP Day 365 values of 28.4%, 35.3%, and 35.3%, respectively). Treatment group differences from the MTX monotherapy group for the abatacept + MTX group at TP Day 169 and TP Day 365 ranged from 12.11 to 14.41.

A small number of subjects in all treatment groups achieved DAS28-CRP remission together with MRI non-progression in erosion, osteitis, or synovitis at 6 months after withdrawal of study drug (WP Day 169). The percentages for the abatacept + MTX group were 12.6%, 15.1%, and 15.1%, compared to the 6.9%, 7.8%, and 7.8%, respectively for the MTX monotherapy group.

Boolean remission

Boolean remission was defined as TJC out of 28 joints ≤1 and SJC out of 28 joints ≤1 and subject global assessment of disease activity (0-10 cm) ≤1 and hsCRP ≤ 1 mg/dL.

At TP Day 365, WP Day 169, and WP Day 365 (Months 12, 18, and 24, respectively), the Boolean rates were 37%, 10%, and 3%, respectively, for the abatacept + MTX group, 27%, 8%, and 4%, respectively, for the abatacept monotherapy group, and 22%, 3%, and 3%, respectively, for the MTX monotherapy group. The treatment differences from MTX monotherapy at the 3 time points (12, 18, 24 months) were 14.56 (95% CI = [2.19, 26.94]), 6.64 (95%CI = [-0.56, 13.83]), and 0.78 (95% CI = [-4.42, 5.97]), respectively, for the abatacept + MTX group.

CDAI

During the Treatment Period, CDAI remission (≤2.8) rates were higher in the abatacept + MTX group than in the MTX monotherapy group beginning at Treatment Period Day 29.

At Month 12, 42% of subjects in the abatacept + MTX group and 31% subjects in the abatacept monotherapy group had achieved CDAI remission compared with 28% of subjects in the MTX monotherapy group (estimated treatment differences of 14.43 [95% CI: 1.55, 27.32] and 3.45 (95% CI: -9.12, 16.02], respectively).

ACR response rates

ACR response rates over time in study IMI01226 are summarised in **Table 9**.

Table 9. ACR20, ACR50, ACR70 and ACR 90 response rates at months 6, 12, 18 and 24 of study IMI01226-ITT population

	Study Day		Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116
ACR20	TP DAY 169	n (%)	86 (72.3%)	76 (65.5%)	65 (56.0%)
		95% CI*	(64.23, 80.31)	(56.87, 74.17)	(47.00, 65.07)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	16.23 (3.29, 29.18)	9.48 (-3.89, 22.85)	N/A
	TP DAY 365	n (%)	89 (74.8%)	74 (63.8%)	76 (65.5%)
		95% CI*	(66.99, 82.59)	(55.05, 72.54)	(56.87, 74.17)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	9.27 (-3.23, 21.77)	-1.72 (-14.89, 11.44)	N/A
	WP DAY 169	n (%)	27 (22.7%)	20 (17.2%)	17 (14.7%)
		95% CI*	(15.16, 30.21)	(10.37, 24.12)	(8.22, 21.09)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	8.03 (-2.72, 18.79)	2.59 (-7.69, 12.86)	N/A
	WP DAY 365	n (%)	13 (10.9%)	8 (6.9%)	12 (10.3%)
		95% CI*	(5.32, 16.53)	(2.29, 11.51)	(4.80, 15.89)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	0.58 (-8.15, 9.31)	-3.45 (-11.52, 4.62)	N/A
ACR50	TP DAY 169	n (%)	64 (53.8%)	44 (37.9%)	40 (34.5%)
		95% CI*	(44.82, 62.74)	(29.10, 46.76)	(25.83, 43.13)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	19.30 (6.00, 32.60)	3.45 (-9.77, 16.67)	N/A
	TP DAY 365	n (%)	76 (63.9%)	62 (53.4%)	54 (46.6%)
		95% CI*	(55.23, 72.50)	(44.37, 62.53)	(37.47, 55.63)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	17.31 (3.94, 30.69)	6.90 (-6.80, 20.60)	N/A
	WP DAY 169	n (%)	20 (16.8%)	18 (15.5%)	10 (8.6%)
		95% CI*	(10.09, 23.53)	(8.93, 22.11)	(3.51, 13.73)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	8.19 (-1.10, 17.48)	6.90 (-2.30, 16.10)	N/A

ACR50	WP DAY 365	n (%)	7 (5.9%)	5 (4.3%)	7 (6.0%)
		95% CI*	(1.65, 10.11)	(0.61, 8.01)	(1.70, 10.37)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	-0.15 (-7.06, 6.75)	-1.72 (-8.28, 4.83)	N/A
ACR70	TP DAY 169	n (%)	43 (36.1%)	30 (25.9%)	21 (18.1%)
		95% CI*	(27.50, 44.77)	(17.89, 33.83)	(11.10, 25.11)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	18.03 (6.06, 30.00)	7.76 (-3.71, 19.23)	N/A
	TP DAY 365	n (%)	63 (52.9%)	45 (38.8%)	40 (34.5%)
		95% CI*	(43.97, 61.91)	(29.93, 47.66)	(25.83, 43.13)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	18.46 (5.15, 31.77)	4.31 (-8.94, 17.56)	N/A
	WP DAY 169	n (%)	13 (10.9%)	13 (11.2%)	7 (6.0%)
		95% CI*	(5.32, 16.53)	(5.47, 16.95)	(1.70, 10.37)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	4.89 (-3.05, 12.83)	5.17 (-2.88, 13.23)	N/A
	WP DAY 365	n (%)	6 (5.0%)	4 (3.4%)	2 (1.7%)
		95% CI*	(1.87, 10.65)	(0.95, 8.59)	(0.21, 6.09)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	3.32 (-2.12, 8.76)	1.72 (-3.22, 6.67)	N/A
ACR90	TP DAY 169	n (%)	17 (14.3%)	8 (6.9%)	3 (2.6%)
		95% CI*	(8.55, 21.88)	(3.02, 13.14)	(0.54, 7.37)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	11.70 (3.93, 19.47)	4.31 (-1.99, 10.61)	N/A
ACR90	TP DAY 365	n (%)	28 (23.5%)	18 (15.5%)	14 (12.1%)
		95% CI*	(15.91, 31.15)	(8.93, 22.11)	(6.14, 18.00)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	11.46 (0.95, 21.97)	3.45 (-6.28, 13.17)	N/A
	WP DAY 169	n (%)	3 (2.5%)	5 (4.3%)	3 (2.6%)
		95% CI*	(0.52, 7.19)	(1.41, 9.77)	(0.54, 7.37)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	-0.07 (-4.95, 4.82)	1.72 (-3.83, 7.28)	N/A
	WP DAY 365	n (%)	5 (4.2%)	2 (1.7%)	1 (0.9%)
		95% CI*	(1.38, 9.53)	(0.21, 6.09)	(0.02, 4.71)
		ESTIMATE OF DIFFERENCE (95% CI) VERSUS MTX	3.34 (-1.49, 8.17)	0.86 (-2.91, 4.63)	N/A

TP= Treatment Period, WP= Withdrawal Period.
N/A= not applicable.
<n = Number of subjects with ACRxx, m = Number of subjects in the analysis.
* Normal approximation is used if the number of ACRxx for all treatment arms is at least 5.
Otherwise an exact method is used.
Continuity correction used for 95% CI of estimate treatment difference.
Imputation rule: missing ACRxx value, not due to premature discontinuation and not at TP Day 1 or WP Day 169, is imputed as a ACRxx if between 2 observed ACRxx.

Time to discontinuation due to lack of efficacy

The median time to discontinuation due to lack of efficacy using this definition was 16.9 months for the abatacept + MTX group and 15.2 months for the MTX monotherapy group, with a hazards ratio of 0.80 (95% CI = [0.5836, 1.0966]). The median time to discontinuation due to lack of efficacy across the entire study was similar for the abatacept monotherapy and MTX monotherapy groups (hazards ratio of 0.95, 95% CI = [0.6885, 1.3182]).

Analysis of the time to discontinuation for lack of efficacy after Month 12 for the subjects who entered the Withdrawal Period also showed a slightly longer median time to discontinuation for the abatacept + MTX group (17.4 months) compared with the MTX monotherapy group (16.1 months), although the hazard ratio for this comparison was 0.91 (95% CI = [0.6212, 1.3192]). The median time to discontinuation for lack of efficacy among subjects who entered the Withdrawal Period was 17.8 months for the abatacept monotherapy group (hazard ratio vs. MTX monotherapy of 0.95, 95% CI = [0.6390, 1.4260]).

Efficacy in the re-exposure period of study IM101226

DAS28-CRP remission during the re-exposure period

In study IM101226, among the 146 subjects who experienced an RA flare and entered the Re-exposure Period, 64 subjects (43.84%) had achieved DAS28-CRP remission after 3 months (at RP Day 85) and 78 subjects (53.42%) had achieved remission by 6 months (RP Day169) following the re-initiation of abatacept + MTX treatment. The remission rates were generally similar based on previous randomized treatment with abatacept + MTX.

The mean DAS28-CRP for all subjects entering the Re-exposure Period was 5.47 (SD 1.27). At the end of the Re-exposure Period (RP Day 169), the change in DAS28-CRP from the start of re-exposure indicated a substantial decrease in disease activity (mean change from start of Re-exposure Period -3.05 [95% CI: -3.34, -2.75]). Improvement was generally similar based on previous randomized treatment

The mean difference in DAS28 CRP score between the abatacept + MTX and MTX monotherapy groups at the end of the Treatment Period (2.07 [SD: 0.58]) was similar to the score at the end of the Re-exposure Period (2.43 [SD: 0.95]).

Re-exposure period HAQ-DI score

Following 6 months of re-treatment with abatacept + MTX, the mean HAQ-DI score had decreased by a mean (SD) of 0.82 (0.07) points, indicating that subjects realized a meaningful improvement in physical function during the 6-month Re-exposure Period.

Summary of main study

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 10. Summary of Efficacy for trial IMI01226

Title: A Phase 3b, randomized, active controlled trial to evaluate the efficacy and safety of abatacept SC in combination with methotrexate in inducing clinical remission compared to methotrexate monotherapy in adults with very early RA		
Study identifier	IM101226	
Design	multicentre, randomized, double-blind, active controlled trial	
	Treatment Period (duration) Withdrawal Period (duration) Re-exposure Period (duration)	12 months 3 to 6 months; up to 12 months for those not entering Re-exposure period 6 months
Hypothesis	Superiority study. Abatacept + MTX is superior to placebo + MTX also in RA patients not previously treated with MTX	
Treatments groups	abatacept + MTX	abatacept SC (125 mg)) weekly + MTX; duration 12 months, number randomized: 119
	abatacept + placebo	abatacept SC (125 mg) SC weekly + MTX placebo; duration 12 month; number randomized: 116
	placebo + MTX	placebo SC + MTX tablets; duration 12 months; number randomized: 116
	Randomisation rate	aba+MTX; aba+placebo; placebo+MTX 1:1:1

Endpoints and definitions	First Co-Primary endpoint	Proportion of subjects at remission (DAS28-CRP < 2.6) at month 12
	Second Co-Primary endpoint	Proportion of subjects at remission (DAS28-CRP < 2.6) at months 12 and 18
	Secondary endpoints	Proportion of in the abatacept monotherapy group in remission DAS28-CRP) at month 12 and at both months 12 and 18
		Proportion of subjects in DAS28-CRP Remission at Month 18 who were in DAS28-CRP LDAS (DAS28-CRP < 3.2) at Month 12
		Proportion of subjects achieving DAS28-CRP Remission over time
		Proportion of subjects achieving a HAQ response (a reduction of at least 0.3 units from baseline in HAQ Disability Index) at Month 12
		Adjusted mean change from baseline over time in DAS28-CRP, adjusted for baseline value and corticosteroid use stratification
		Proportion of subjects achieving SDAI-defined remission criteria of ≤ 3.3 at month 12 and at Month 18
		Adjusted mean change from baseline over time in SDAI
		Proportion of subjects with a HAQ response (defined as a reduction from baseline in HAQ-DI of at least 0.3 points) over time
		Adjusted mean change from baseline over time in HAQ-DI
		Adjusted mean change from baseline in erosion, synovitis and osteitis scores based on MRI scoring at study Months 6, 12, and 18.
I Database lock	month 18	
II Database lock	month 24	
Results and Analysis		
Analysis description		

<table>
<tr><td>Analysis population and time point description</td><td colspan="4">Efficacy and safety data from all subjects were analyzed according to the treatment group assignment in accordance with the randomization schedule.

Treatment period
The ITT and All Treated Subjects analysis populations for the Treatment Period were identical and included all randomized subjects who received at least 1 dose of double-blind study medication in the Treatment Period
Populations Analyzed: 351 subjects (119 in the abatacept + MTX group, 116 in the abatacept monotherapy group, and 116 in the MTX monotherapy group).

The overall Immunogenicity analysis population included 224 subjects treated with abatacept SC who had at least 1 immunogenicity sample during the study period (116 in the abatacept + MTX group and 108 in the abatacept monotherapy group.

Withdrawal period
The All Treated Subjects Entering the Withdrawal Period analysis population included 225 subjects who had entered the Withdrawal Period (84 in the abatacept + MTX group, 66 in the abatacept monotherapy group, and 75 in the MTX monotherapy group).

Re-exposure period
The All Treated Subjects Entering the Re-exposure Period analysis population included 146 subjects who had entered the Re-exposure Period (55 in the abatacept + MTX group, 48 in the abatacept monotherapy group, and 43 in the MTX monotherapy group).</td></tr>
<tr><td rowspan="11">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>Abatacept + MTX</td><td>Abatacept</td><td>MTX</td></tr>
<tr><td>Number of subject, n (%)</td><td>119</td><td>116</td><td>116</td></tr>
<tr><td colspan="4">Treatment Period</td></tr>
<tr><td colspan="4">Improvement of Signs and Symptoms of RA – remission</td></tr>
<tr><td>n of subjects (%) in remission (DAS28-CRP) <2.6 at 12 months</td><td>70/115

(60.9)</td><td>48/113

(42.5)</td><td>52/115

(45.2)</td></tr>
<tr><td>n of subjects (%) in remission (DAS28-CRP) < 2.6 at both 12 and 18 months</td><td>17/115

(14.8)</td><td>14/113

(12.4)</td><td>9/115

(7.8)</td></tr>
<tr><td>Adjusted mean change from baseline in DAS28-CRP at month 12 (SE)

Treatment difference (95% CI)</td><td>-3.09 (0.13)

– 0.50
(-0.85, -0.15)</td><td>-2.75 (0.13)

– 0.16
(-0.52, 0.20)</td><td>– 2.58 (0.13)

N/A</td></tr>
<tr><td>ACR/EULAR Boolean remission rates at month 12</td><td>37%</td><td>27%</td><td>22%</td></tr>
<tr><td>SDAI</td><td></td><td></td><td></td></tr>
</table>

n (%),proportion of subjects achieving SDAI-(corrected) defined remission criteria of ≤ 3.3 at Month 12 Aba-MTX treatment difference (95% CI)	50 42.0% 17.02 (4.30, 29.73)	34 29.3% 4.31 (-7.98, 16.61)	29 25.0% N/A
Adjusted mean change from baseline over time in SDAI (corrected) at 12 months	-31.24	-28.88	-28.34
proportion of subjects achieving CDAI-(corrected) defined remission criteria of ≤ 3.3 at Month 12	42% Aba-MTX treatment difference 14.43 (1.55, 27.32)	31% 3.45 (-9.12,16.02)	28% N/A
Physical function			
The proportion of subjects in achieving a HAQ response at Month 12, as measured by a reduction of at least 0.3 units from baseline in HAQ Disability Index (HAQ-DI)	80 67,2% Aba-MTX treatment difference 23.26 95% CI (10.05, 36.47)	61 52.6% 8.63 95% CI (-5.05, 22.29	51 44.0% N/A
Adjusted mean change from baseline over time in HAQ-DI month 12	-0.87	-0.73	-0.72
Structural damage			

	Adjusted mean change from baseline (SE) (95% CI) erosion score, synovitis score and osteitis scores based on MRI scoring at 12 months	0.34 (0.35) (-0.35, 1.04) treatment differences -1.22 (-2.20, -0.25) -2.38 (0.29) (-2.96, -1.80) treatment differences -1.60 (-2.42, -0.78) -2.32 (0.46) (-3.22, -1.43) Treatment differences -1.43 (-2.68, -0.18)	1.57 (0.36) (0.87, 2.27) 0.01 (-0.97, 0.99) -1.36 (0.30) (1.96, -0.77) -0.59 (-1.43, 0.24) -1.30 (0.46) (-2.21, -0.39) -0.4. (-1.66, 0.86)	1.56 (0.36) (0.86, 2.27) N/A -0.77 (0.30) (-1.37,-0.18) N/A -0.90 (0.46) (-1.81, 0.02) N/A
	Treatment group	abatacept + MTX	abatacept +placebo	placebo + MTX
Withdrawal Period (at 18 months)				
	Number of subject entered withdrawal, n (%)	84	66	75
	Signs and Symptoms of RA – remission			
	n, (%) in **remission** over time (DAS28-CRP) <2.6 over time at **18 months** Aba-MTX treatment difference	19 (26.0%) 9.05 (-6.85, 24.94)	15 (30.0%) 13.02 (-5.16, 31.20)	9 (17.0%) N/A
	n, (%) in **remission** over time (DAS28-CRP) < 2.6 **24 months**	9 (12.3%) 1.01 (-12.01, 14.02)	7 (14.0%) 2.68 (-12.12, 17.48)	6 (11.3%) N/A
	Adjusted mean change from baseline in DAS28-CRP at month 18 (SE) Treatment difference (95% CI)	41 -1.54 (0.26) – 0.48 (-1.24, 0.28)	31 -1.51 (0.29) – 0.46 (-1.27, 0.36)	32 -1.06 N/A
	SDAI			

	n (%), proportion of subjects in SDAI-(corrected) defined remission criteria of ≤ 3.3 over time at Month 18 Aba-MTX treatment difference (95% CI)	14 (11.8%) 4.87 (-3.38, 13.12)	11 (9.5%) 2.59 (-5.32, 10.50)	8 (6.9%) N/A
	Physical function			
	n, (%) proportion achieving a HAQ response at Month 18, as measured by a reduction of at least 0.3 units from baseline in HAQ Disability Index (HAQ-DI)	27 (22.7%) treatment difference 12.34 (2.15, 22.54)	19 (16.4%) 6.03 (-3.55, 15.62)	12 (10.3%) N/A
	the adjusted mean changes from baseline in the HAQ-DI score	-0.52	-0.49	-0.33
	n, (%) achieving a HAQ response at 6 months after withdrawal of all study medication, as measured by a reduction of at least 0.3 units from baseline in HAQ Disability Index (HAQ-DI)	22.7% treatment difference (95% CI) 12.34 (2.15, 22.54)		10.3%;
	Structural damage			

	Adjusted mean change from baseline (SE) (95% CI) erosion score, synovitis score and osteitis scores based on MRI scoring at 18 months	0.20 (0.47) (-0.74, 1.14) -1.71 (0.45) (-2.59, -0.82) -1.94 (0.88) (-3.68, -0.20)	2.16 (0.48) (1.21, 3.11) 0.98 (0.89) (-0.79, 2.74)	1.89 (0.50) (0.90, 2.87) -0.71 (0.49) (-1.68, 0.27) -0.33 (0.96) (-2.24, 1.58)
		treatment difference -1.69 (-3.04, -0.33) treatment difference -1.00 (-2.31, 0.31) treatment difference – 1.61 (-4.18, 0.95)	0.28 (-1.08, 1.64) -0.25 (-1.57, 1.07) 1.31 (-1.28, 3.89)	N/A N/A N/A
	Adjusted mean change from baseline over time in SDAI at month 18	-17.43	-19.13	-13.64
Re-exposure period				
	Treatment group	Abatacept + MTX n =55	Abatacept n=48	MTX n=43
	n (%) of subjects (all treated) in **remission** over time (DAS28-CRP) <2.6 at RP d85 Treatment difference	23 (41, 82%) (28.78, 54.85) – 2.37 (-24.19, 19.46)	22 (45.83 %) (31.74, 59.93) 1.65 (-21.03, 24.32)	19 (44.19 %) (29.34, 59.03) N/A
	n (%) of subjects (all treated) in **remission** over time(DAS28-CRP) < 2.6 at RP d169 Treatment difference	27 (49.09 %) (35.88, 62.30) – 2.07 (-24.09, 19.94)	29 (60.42 %) (46.58, 74.25) 9.25 (-13.31, 31.82)	22 (51.16 %) (36.22, 66.10) N/A

	proportion of subjects in achieving a HAQ response after 6 months of retreatment, as measured by a reduction of at least 0.3 units from baseline in HAQ Disability Index (HAQ-DI)	Start of treatment: 26% Post 3 months: 67% Post 6 months: 59% Mean decrease in HAQ-DI score 0.8 points (range 0-3)		

Effect estimate per comparison			
First Co-Primary endpoint	abatacept + MTX n = 119	abatacept + placebo n = 116	placebo + MTX n = 116
DAS28CRP at 12 months, n/m (%)	70/115 (60.9)	48/113 (42.5)	52/115 (45.2)
Odds ratio	2.01	0.92	N/A
95% CI	(1.18, 3.43)	(0.55, 1.57)	
p value (log regression model)	0.010	N/A	N/A
Second Co-Primary endpoint DAS28CRP at both 12 and 18 months, n/m (%)	abatacept + MTX n = 119	abatacept + placebo n = 116	placebo + MTX n = 116
	17/115 (14.8)	14/113 (12.4)	9/115 (7.8)
Odds ratio	2.51	2.04	N/A
95% CI	(1.02, 6.18)	(0.81, 5.14)	N/A
p value (log regression model)	0.045	N/A	N/A
Secondary endpoints	None performed**	None performed	None performed
Notes	*p values from a logistic regression model that included treatment, baseline DAS28-CRP value, and stratification factor of corticosteroid use at BL as explanatory variables ** no formal statistical testing was performed for any secondary or exploratory efficacy endpoints		

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

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive studies

In addition to the pivotal study, results from study IM101023 (the AGREE study), and available comparative data in MTX-naive patients treated with adalimumab, tocilizumab and abatacept were also submitted in support of this application.

Summary of design and methods

Study IM101023 (previously evaluated by the CHMP during EMEA/H/C/ 000701/II/0033) was a multi-centre, randomized, double-blind, 2-arm parallel-dosing study, designed to evaluate the efficacy and safety of abatacept IV+ MTX in MTX-naïve subjects with early, erosive RA. This 2-year study, with 1 year of double-blind treatment followed by 1 year of single-blind, open-label treatment, randomized subjects in a 1:1 ratio to receive abatacept approximately 10 mg/kg, weight-tiered dose) + MTX (dose titrated to at least 15 mg per week, not to exceed 20 mg per week) or IV placebo + MTX for the first 12 months of treatment. All subjects who continued into the second year of treatment received open-label abatacept with a background of MTX for 12 months; the original placebo + MTX group was switched to abatacept in the second year.

Overall study methods were similar in study IM101023 to study IM101226. The Randomised population was the same as the All Treated population: there were 509 subjects total (256 in the abatacept + MTX group and 253 in the placebo + MTX group).

The co-primary objectives for study IM101023 during the initial 12-month blinded period were to compare the clinical efficacy of abatacept used in combination with MTX vs placebo + MTX on the following: the proportion of subjects who achieved remission at Month 12 of treatment, as defined by a DAS28-C-reactive Protein (CRP) score < 2.6 Joint damage progression measured by radiographic evaluation using the Genant-modified Sharp total score at Month 12. During the second-year, Open-label Period, the primary objectives were to evaluate long-term safety and tolerability of abatacept + MTX. Secondary objectives included assessments of physical function using the HAQ disability index and inhibition of joint damage progression measured by radiographic evaluation using the Genant-modified Sharp scores (for erosion, JSN, and total score) at Month 24.

Summary of results:

The baseline demographic characteristics were similar for both treatment groups (abatacept + MTX and placebo + MTX). The majority of subjects were white females, men age approximately 50 years old.

In study IM101023, the baseline clinical RA characteristics were similar for both groups (**Table 11**).

Table 11. Baseline disease characteristics in Study IMI01023 (All randomised and treated subjects)

	IMI01023 Abatacept+ MTX N = 256	IMI01023 Placebo + MTX N = 253
SUBJECT GLOBAL ASSESSMENT	256	252
	65.8	63.7
	21.8	24.0
	69.9	66.7
	3.0	2.0
	99.0	100.0
PHYSICIAN GLOBAL ASSESSMENT	255	253
	67.1	65.7
	18.2	18.9
	69.0	67.0
	13.4	13.4
	100.0	98.0
CRP	256	253
*mg/L	3.1**	3.6**
**mg/dL	3.1	5.0
	2.0	2.1
	0.0	0.1
	15.8	58.0
RHEUMATOID FACTOR STATUS	9 (3.5%)	7 (2.8%)
	246 (96.1%)	245 (96.8%)
DAS28-CRP	256	252
	6.3	6.2
	1.0	1.0
	6.3	6.3
	3.8	2.1
	8.4	8.2

Baseline is Day 1 of the study
Note: Per Inclusion Criteria, ts were not ACPA positive, which were protocol deviations.
Source: Table 5.3.2-1 and Sect'inal CSR (1 year)[3]

Antirheumatic medications prior to screening were similar between treatment groups. Subjects were allowed prior MTX exposure of 10 mg per week for not more than 3 weeks and no dose for 3 months prior to signing the informed consent. In study IM101023, only 2% of subjects received prior treatment with MTX. Approximately half of subjects received prior treatment with oral and/or injectable corticosteroids. NSAID use prior to treatment was reported in 77% of subject in the abatacept + MTX group.

In study IM101023, concomitant (or rescue) corticosteroid use was similar to study IM101226. At Day 1, 31.6% of subjects in the abatacept + MTX group and 28.5% of subjects in the MTX group reported prednisone use. During the first 12 months of the study, 58.6% subjects in the abatacept + MTX group and 62.5% of subjects in the MTX group reported oral and/or injectable corticosteroid use. The proportion of subjects who received corticosteroids (oral and/or injectable) was comparable for both groups during the open-label period and similar to that observed in the double-blind period.

Two (2) subjects were randomized but not treated. The most frequent reasons for not being randomized were subjects no longer met study criteria, the subject withdrew informed consent, and “other”. Discontinuations due to death were comparable between the 2 groups (2 subjects in each group). A total of 232 (90.6%) subjects in the abatacept + MTX group and 227 (89.7%) subjects in the placebo + MTX group completed the first year of the study.

All 459 subjects who completed the double-blind period were treated in the Open-label Period. Few subjects (26 [5.7%] subjects) discontinued from the Open-label Period; the most common reason for discontinuation was AE (11 [2.4%] subjects; 4 subjects in the original abatacept + MTX group and 7 subjects in the original placebo + MTX group). In addition, 2 subjects died (1 subject from each original treatment group). A total of 433 (94.3%) subjects completed the Open-label Period of the study.

Outcomes

Analysis of the primary efficacy variable for study IM101023 demonstrated that the percent of subjects achieving remission, as defined by DAS28-CRP < 2.6, at Month 12 was significantly higher in the abatacept + MTX group compared with the placebo + MTX group (41.4% versus 23.3%, p < 0.001)/

The main efficacy findings from the AGREE study are summarised in **Table 12**.

Table 12. Proportion of subjects with DAS28-CRP remission and HAQ-DI response at month 12 in the AGREE study (All randomised and treated subjects)

	AGREE	
Efficacy Endpoint	**Abatacept + MTX N = 256[a]**	**MTX N = 253[b]**
DAS28-CRP < 2.6, n/m (%)	106/256 (41.4)	59/253 (23.3)
AVERT: Odds ratio (95% CI) vs. MTX; AGREE: Estimate of difference vs MTX (95% CI)	18.1 (9.6, 26.6)	NA
P value	<0.001	NA
SDAI ≤ 3.3, AVERT: n (%); AGREE: n/m (%)	70/210 (33.3)	26/209 (12.4)
95% CI	27.0, 39.7	8.0, 16.9
Estimate of difference vs MTX (95% CI)	NA	NA
CDAI ≤ 2.8, AVERT: n (%); AGREE: n/m (%)	72/210 (34.3)	34/209 (16.3)
95% CI	27.9, 40.7	11.3, 21.3
Estimate of difference vs MTX (95% CI)	NA	NA
Boolean Remission[c], AVERT: n (%); AGREE: n/m (%)	50/210 (23.8)	12/209 (5.7)
95% CI	18.0, 29.6	2.6, 8.9
Estimate of difference vs MTX (95% CI)	NA	NA
HAQ-DI, n (%)	184 (71.9%)	157 (62.1%)
95% CI	66.4, 77.4	56.1, 68.0
Estimate of difference vs MTX (95% CI)	9.8 (1.3, 18.4)	NA

Abbreviations: n = Number of subjects with DAS28-CRP Remission at Month 12, m = Number of subjects in the analysis, MTX = methotrexate, NA = not applicable.
Note: AVERT -Odds ratio and p-values are based on an Adjusted Logistic Regression test, including treatment (3 groups), baseline DAS28-CRP values as well as the stratification factor (corticosteroid use at baseline). Normal approximation is used if the number of SDAI/CDAI/Boolean Remission for all treatment arms is at least 5. Otherwise an exact method is used. Continuity correction used for 95% CI of estimate treatment difference. Imputation rule: missing SDAI/CDAI/Boolean Remission value, not due to premature discontinuation and not at TP Day 1 or WP Day 169, is imputed as a Remission if between 2 observed Remission.
- AGREE - P-value is based on a continuity corrected chi-square test; probability for testing the difference between abatacept and placebo. [a]Ad hoc analysis based on available data from 210 abatacept + MTX subjects.
[b]Ad hoc analysis based on available data from 209 MTX monotherapy subjects.
[c]Boolean Remission Criteria is defined as Tender joint counts out of 28 joints <=1 and Swollen joint counts out of 28 joints <=1 and Subject global assessment of disease activity (0-10cm) <=1 and hsCRP <= 1 mg/dL.

X-ray imaging was used to evaluate joint damage using a scoring technique based on the Genant-modified Sharp algorithm. Of the 509 subjects randomized and treated, 506 (99%) subjects had radiographic data collected at minimally 1 time point during the study. There were 484 (95%) subjects included in the primary radiographic analysis with data at both baseline and post-baseline (on Month 6, Month 12, and /or on the day of discontinuation).

This analysis revealed that subjects in the abatacept + MTX group had significantly less progression of structural damage compared with the placebo + MTX group as demonstrated by the mean change from baseline in total score at Month 12 (p = 0.040;) and over time using a Cumulative Distribution Function Plot. The mean change from baseline in total scores at Month 12 for the abatacept + MTX group (0.63) was less than that in the placebo + MTX group (1.06).

Post Hoc Analyses by disease activity at baseline

Similar to the results from Study IM110226, subjects from study IM101023 were also analysed by disease activity at baseline (**Table 13**).

Table 13. Study IM101023 - Proportion of Subjects with DAS28-CRP Remission at Month 12 by Baseline Characteristic Factors - ITT Population

AGREE		Abatacept + MTX N = 256	MTX N = 253
Baseline DAS28CRP	MISSING	0	1 (0.04%)
	LDAS	0	2 (0.08%)
	MDAS	31 (12.1%)	25 (9.9%)
	HDAS	225 (87.9%)	225(88.9%)

Baseline is Day 1 of the study. LDAS is defined as DAS28-CRP < 3.2, MDAS is defined as 3.2 <= DAS28-CRP <= 5.1 and HDAS is defined as DAS28-CRP > 5.1.

Analysis of the proportion of subjects with DAS28-CRP remission at Month 12 by disease activity is shown in **Table 14**.

Table 14. Study IM101023 - Proportion of Subjects with DAS28-CRP Remission at Month 12 by Baseline Characteristic Factors - All Randomized and Treated Subjects

Baseline DAS28-CRP		Abatacept + MTX N=256	MTX N=253
Missing	Number of subject n/m (%)	0	0/1 (0.0%)
	95% CI*	(0.00, 0.00)	(2.50, 100.00)
	Est. of Diff. vs. MTX (95% CI)	NE	N/A
< 3.2	Number of subject n/m (%)	0	0/2 (0.0%)
	95% CI*	(0.00, 0.00)	(15.81, 100.00)
	Est. of Diff. vs. MTX (95% CI)	NE	N/A
>= 3.2 and <=5.1	Number of subject n/m (%)	16/31 (51.6%)	7/25 (28.0%)
	95% CI*	(34.02, 69.20)	(10.40, 45.60)
	Est. of Diff. vs. MTX (95% CI)	23.6 (-5.9, 53.1)	N/A
> 5.1	Number of subject n/m (%)	91/225 (40.4%)	53/225 (23.6%)
	95% CI*	(34.03, 46.86)	(18.01, 29.10)
	Est. of Diff. vs. MTX (95% CI)	16.8 (7.7, 25.9)	N/A

Abatacept efficacy comparisons with anti-TNF agents

The ATTEST study examined the safety and efficacy of IV abatacept or infliximab relative to placebo, all on a background of MTX, in a MTX-IR population. The AMPLE study compared, in a 2 year head-to-head study, the efficacy and safety of SC abatacept and adalimumab, with background MTX, in patients with moderate to severely active MTX-IR RA population with mean disease duration of less than 2 years.

The PREMIER and FUNCTION studies were 2 large RCTs that compared adalimumab + MTX or tocilizumab + MTX, respectively, to MTX monotherapy in subjects with early RA, naive to therapy with MTX. The proportion of the subjects achieving remission and the ACR response rates from these studies are summarised in **Table 15**.

Table 15. Proportion of subjects achieving DAS28-defined remission and ACR response at 1 year in Randomised controlled trials: AVERT, AGREE, PREMIER and FUNCTION

	AVERT			AGREE		
DAS28-defined Remission	Abatacept + MTX	MTX	Effect Size[a]	Abatacept + MTX	MTX	Effect Size[a]
DAS28-CRP < 2.6, (%)	60.9	45.2	15.7	41.4	23.3	18.1
ACR (%)						
ACR 20	74.8	65.5	9.3	76.2	62.1	14.1
ACR 50	63.9	46.6	17.3	57.4	42.3	15.1
ACR 70	52.9	34.5	18.4	42.6	27.3	15.3
ACR 90	23.5	12.1	11.4	16.4	6.7	9.7

	PREMIER			FUNCTION				
							Effect Size[a]	
DAS28-defined Remission	Adalimumab + MTX	MTX	Effect Size[a]	Tocilizumab 8 mg/kg + MTX	Tocilizumab 4 mg/kg + MTX	MTX	Toc8	Toc4
DAS28-CRP < 2.6, (%)	43.0	21.0	22.0	49.0	34.0	19.5	29.5	14.5
ACR (%)								
ACR 20	72.8	62.6	10.2	67.2	62.8	57.1	10.1	5.7
ACR 50	61.6	45.9	15.7	55.9	52.4	40.8	15.1	11.6
ACR 70	45.5	27.2	18.3	43.1	37.2	28.9	14.2	8.3
ACR 90	24.0	13.0	11.0	NA	NA	NA	NA	NA

DAS28 = Disease Activity Score-28; CRP = C-reactive protein; MTX = methotrexate; ACR = American College of Rheumatology; Toc8 = Tocilizumab 8 mg; Toc4 = Tocilizumab 4 mg; NA = not applicable.

[a]Effect Size = combination therapy effect – MTX monotherapy effect.

2.4.3. Discussion on clinical efficacy

The initial scope of this application was to extend the current indication of sc and iv abatacept in combination with MTX in the treatment of adults with moderate to severe RA who responded inadequately to previous therapy with one or more DMARDs, to the treatment of adults who have highly active disease with poor prognostic factors (such as ACPA+ and/or RF+, joint erosion) not previously treated with MTX. Several clinical, laboratory and imaging features have been associated with aggressive disease or poor outcome in RA. The MAH initially chose 'ACPA+ and/or RF+, joint erosion' as examples of factors with poor prognosis, to define the intended target population. Even though there is evidence that RF and ACPA positivity can serve as poor prognostic factors in RA, the validity of these factors as predictors of a poorer outcome was however, not considered to be unambiguously clear. On the other hand, the nature and the severity of the studied patient population were substantiated by radiology measurements. The high MRI baseline mean values indicated that patients had significant joint erosion i.e. had an active progressive disease already at this early stage of the disease. Therefore, the revised indication for the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with methotrexate was considered appropriate by the CHMP.

Efficacy was assessed in a single pivotal controlled clinical trial IM101226 (AVERT). The study compared abatacept in combination with MTX to MTX monotherapy and in a third arm to abatacept monotherapy. The aim was to show higher proportion of remission on the pre-specified co-primary endpoint of remission at 12 months, and at both 12 and 18 months, for abatacept in combination with MTX compared to MTX monotherapy. The supportive evidence for this claim includes study IM101023 (AGREE) and efficacy comparisons with anti-TNF agents (studies AMPLE IM1012358, and ATTEST IM1010439). The results of AGREE, AMPLE and ATTEST studies have been previously submitted and evaluated.

Design and conduct of the pivotal clinical study

The pivotal study IM101226 was a phase IIIb, randomised, active controlled trial to evaluate the efficacy and safety of abatacept sc in combination with methotrexate in inducing clinical remission compared to the active controls, methotrexate monotherapy and abatacept monotherapy, in adults with very early RA.

Subjects with early disease (persistent symptoms for less than 2 years) with poor prognostic factors (seropositive, structural joint damage) were enrolled. Criteria of RA according to 2010 ACR/EULAR recommendations were not required at inclusion. However, as the inclusion criteria of the pivotal study closely correlated with the ACR/EULAR criteria, it was considered that the target population was appropriate. Subjects had to be MTX-and biologic-naive and have a minimum of 3.2 points on DAS28-CRP score. In the AGREE study, subjects having RA-diagnosis for less than 2 years were enrolled.

In study IM101223, stable, low-dose steroid was permitted. The co-primary endpoints were DAS-defined remission rates (DAS28-CRP < 2.6) at Month 12 and at both Month 12 and Month 18. Other endpoints included other standard measures of disease activity (ACR-response rates, Boolean remission, SDAI, CDAI), physical function (HAQ-DI), and structural damage (MRI, using OMERACT RAMRIS scoring).

The study comprised three periods: the Treatment Period, The Withdrawal Period and the Re-exposure Period. Randomization was stratified according to corticosteroid use (yes/no) at baseline. The co-primary efficacy endpoints were assessed at the end of the Treatment Period (12 months) and after 6 months of the Withdrawal Period (at both 12 and 18 months).

Statistics and analysis sets

Efficacy Analyses: The analyses for the 2 co-primary efficacy endpoints were performed using the intent-to-treat (ITT) analysis population by randomized treatment group. These analyses involved a comparison of the abatacept + MTX group and the MTX monotherapy group using a logistic regression test adjusting for baseline and corticosteroid use at baseline. The odds ratio estimate, corresponding 95% confidence interval (CI), and p-value for the 2 comparisons were provided. The statistical testing was conducted in a hierarchical fashion to maintain the overall Type I error rate at 5%. For the first co-primary endpoint, all subjects who prematurely discontinued the study for any reason were considered not to have achieved remission.

The other secondary endpoints were also analyzed using the ITT population. The method used for response rates were point estimates and 95% CI of treatment difference. The 95% CIs for a response rate within treatment group were based on normal approximation, provided there were at least 5 events in each treatment group; otherwise, the exact method was used. The 95% CI for treatment difference in response rate was constructed using the continuity correction. The method used for continuous secondary endpoints was a longitudinal repeated measures analysis adjusting for baseline and corticosteroid use at baseline including the observed data at all time points. The adjusted means, standard error and 95% CI for adjusted mean difference between treatment groups (abatacept + MTX group vs. MTX monotherapy group) were provided. All CIs were 2-sided.

No concerns were raised on the integrity of the blinding and the randomisation procedure was considered acceptable.

Given the small number of subjects with relevant deviations, per-protocol analyses were not conducted. Baseline demographics and disease characteristics were well-balanced across the three treatment arms suggesting a successful randomisation. Discontinuation during treatment period was generally low (17.4%) and the lowest in the combination group (13%). Discontinuation due to lack of efficacy was the highest in the MTX mono-arm (9.5%) and the lowest in the combination group (4.2%).

Overall, no major concerns were raised on the conduct of the study.

Efficacy data and additional analyses

Co-primary efficacy analysis

In the treatment period, on the first co-primary end point, the proportions of RA subjects in remission at month 12 compared to treatment with MTX alone were respectively: 60.9 % vs 45.2 %, OR (95% CI) 2.01 (1.18 3.43), p<0.01. The endpoint is a clinically relevant one for a MTX naïve RA population. The therapeutic effect was clear with an effect size comparable or even better than the MAH previous data in MTX-naïve patients. On the second co-primary endpoint of remission at both 12 and 18 months (Withdrawal Period) significantly higher rates of sustained remission after withdrawal of all RA therapy (Month 18) was also seen: 14.8 % vs 12.4% OR (95% CI) 2.51 (1.02 6.18) p< 0.045, but the results appeared of borderline significance. These findings on the co-primary end point showed that complete withdrawal of all study medications leads to relapse of remission in the majority of the patients.

Furthermore, consistent *post hoc* analysis of efficacy across different subpopulations showed that results were not driven by a particular patient subgroup (e.g. by baseline disease severity, RA diagnosis, time since RA diagnosis or persistence of symptoms, by presence of erosion at baseline, gender, region and age). Especially in relation to baseline disease activity, there was no difference between patients with moderate disease activity at baseline (DAS-28 CRP between 3.2 and 5.1) and those with high baseline disease activity (DAS-28 CRP > 5.1).

Secondary analyses

A large number of secondary end points were analysed, however, it must be noted that no formal statistical analyses were performed on any of these variables. Superior efficacy of the combination to MTX is supported by a number of secondary endpoints of disease activity. However, DAS-remission, change from baseline DAS-scores and Boolean-remission, analysis show the same pattern: efficacy was evident at month 12, but the difference of the combination to MTX is not significant at 6 months following discontinuation of therapy.

Withdrawal period

The results of the withdrawal period showed a small, but significantly greater number of subjects achieving drug-free, DAS-defined remission. This effect however was likely not due solely to the long-term effects of abatacept, as assessments were performed up to 12 months after the withdrawal of all treatment (> 5 half-lives) and were more pronounced for abatacept+MTX than for abatacept monotherapy.

Furthermore, a *post hoc* analyses showed that the risk of having a relapse after withdrawal of all study medications, including MTX, was similar across the three study groups. Therefore it was concluded that in this study population drug withdrawal leads to relapse of remission in the majority of the patients irrespective of treatment.

Structural damage

Use of MRI, instead of plain radiographs, to evaluate of structural damage, both as a response and as an inclusion criterion reflected in the indication, has so far been less common in RA clinical trial, at least in the EU regulatory setting. According to regulatory and ACR/EULAR clinical guidance it is recommended that in clinical trials structural bone damage should be reported by x-rays. CHMP guidance considers MRI as a supportive tool. In the pivotal AVERT study of the current Application no radiographs were taken. Instead MRI data of the joints was accrued.

The MAH, however, argued that joint damage – both synovitis and bone changes such as bone oedema or bone cysts- can be detected within weeks of the onset of symptoms more sensitively using MRI or ultrasound. Radiographic erosions were visualised when bone decalcification occurred, and a lag time between the onset of synovitis and radiographic bone erosion has been recognised. In contrast, MRI can detect synovitis and earlier bone lesions such as bone marrow inflammation (bone oedema) which may be a forerunner (or at least equivalent) of radiographic erosions (McGonagle et al, 1999).

The IM101102 study (Study II17) was first to demonstrate benefit to structural joint damage over 5 years of therapy with IV abatacept + MTX in subjects with an inadequate response to MTX. Study IM101023 (Study VI) reproduced the benefits of IV abatacept on structural joint damage over 24 months in a MTX-naive, early RA population. Study IM101235 (Study SC-II20) then demonstrated the benefits of SC abatacept + MTX on inhibition of structural joint damage over a 2-year blinded treatment period in a head-to-head comparison with adalimumab + MTX in subjects with an inadequate response to MTX with a mean disease duration of less than 2 years.

Structural damage in the pivotal AVERT study:

MRI measures were performed to assess change from baseline joint erosion and inflammation (osteitis and synovitis). Even though inclusion criteria did not include any baseline joint erosion measure, high MRI baseline mean values clearly indicated that the studied population had significant joint erosion. Change from baseline in erosion and inflammation scores showed that joint damage progressed slower and inflammation decreased more in the combination arm compared to monotherapy arms, as reflected by mean post baseline MRI erosion score, and larger improvements in MRI osteitis and synovitis scores at month 12 compared with the MTX monotherapy group. The treatment difference in MRI erosion scores favoring the abatacept + MTX group persisted 6 months after withdrawal of study treatment.

Structural damage in the supportive AGREE study:

At the time of the initial assessment of this supportive study the size of the radiological abatacept treatment effect as measured by radiographs appeared small and comparisons to other therapies could not be fully estimated, which argued against the use of abatacept as first-line monotherapy. In this study, the second structural co primary end point showed consistent results with the first primary outcome, but some reservations on the size of the effect and the statistical analyses on this outcome were raised. It was subsequently shown that the results on this endpoint were not sensitive to the choice of the statistical analysis method, but that the magnitude of the effect appeared small. Evaluation of joint damage was carried out using the Genant modified Sharp score, which is well documented in many clinical studies as a robust tool. According to the results of the long term follow-up of this trial, radiographic progression remained stable over the observation period.

Even though there are still some uncertainties regarding these results as no formal statistical analyses were performed on this outcome and only descriptive statistics were available, the CHMP agreed that overall abatacept treatment has a positive effect in reducing structural damage as the abatacept + MTX group had significantly less progression in structural damage compared with MTX group as reflected by mean treatment difference of the abatacept + MTX group versus MTX group. Furthermore, a difference between the two treatment groups could be observed after 6 months of the complete drug withdrawal.

Re-exposure

During the re-exposure period all the 146 patients were treated with the combination (abatacept+MTX). Both DAS-remission rates and mean change from baseline values were comparable to those in the treatment period. Remission rates and mean decrease in DAS-scores were similar across all prior treatment arms confidence intervals overlapped.

Withdrawal

In the pivotal study it was shown that complete withdrawal of all study medications led to relapse of remission in the majority of the patients, with the requested *post hoc* analyses showing that the risk of having a relapse after drug withdrawal was similar across the three study groups.

Comparison of abatacept with TNF-inhibitors

Abatacept has been studied in 2 trials with anti-TNF agents as a reference arm or as a comparator.

Infliximab

The ATTEST study (IM101043; Study V in the SmPC) examined the safety and efficacy of IV abatacept or infliximab relative to placebo, all on a background of MTX, in a MTX-IR population. Greater improvement ($p < 0.001$) in DAS28 was observed with abatacept and with infliximab compared to placebo at six months in the placebo controlled portion of the trial; the results between the abatacept and infliximab groups were similar. The ACR responses in Study V were consistent with the DAS28 score.

Adalimumab

The AMPLE study (IM101235; Study SC-II in the SmPC) compared, in a 2 year head-to-head study, the efficacy and safety of SC abatacept and adalimumab, with background MTX, in patients with moderate to severely active MTX-IR RA population with a mean disease duration of less than 2 years.

The primary endpoint showed non-inferiority (predefined margin of 12%) of ACR 20 response after 12 months of treatment, 64.8% (206/318) for the abatacept SC group and 63.4% (208/328) for the adalimumab SC group; treatment difference was 1.8% [95% confidence interval (CI): -5.6, 9.2], with comparable responses throughout the 24-month period. The respective values for ACR 20 at 24 months were 59.7% (190/318) for the abatacept SC group and 60.1% (197/328) for the adalimumab SC group. The respective values for ACR 50 and ACR 70 at 12 months and 24 months were consistent and similar for abatacept and adalimumab.

Across-study comparison (adalimumab, tocilizumab)

The effect sizes were mostly comparable amongst the different biologics, with the exception of a higher effect size of tocilizumab 8 mg/kg + MTX versus other biologics on the DAS28-CRP <2.6 measure. However, this difference is specific to this measure and the mechanism of action of tocilizumab (i.e. IL-6 antagonism that affects CRP more than other biologics), which is highlighted by the lack of differences on other endpoints (e.g. ACR scores or remission endpoints). Specifically, the effect size with abatacept + MTX versus MTX monotherapy in AVERT for SDAI and Boolean remission measures at Week 52 (17% and 15%, respectively) are similar to those observed with tocilizumab 8 mg/kg + MTX versus MTX in the FUNCTION trial (13.7% and 10.2%, respectively). Despite the limitations of comparison different studies, these data may provide additional evidence that when used in combination with MTX, abatacept, adalimumab, and tocilizumab provide comparable efficacy in MTX-naive early RA patients.

2.4.4. Conclusions on the clinical efficacy

The main study IM101226 (AVERT) has provided results which support a clinically meaningful efficacy of sc abatacept in combination with MTX in MTX-naïve RA population with highly active disease, in terms of disease activity, physical function and structural damage of the joint. These results confirm the results of the previously submitted IM101023 study (AGREE, also in MTX-naïve, RA-patients).

Furthermore, across-study comparisons of effect sizes in MTX-naïve population show that combination of MTX with abatacept, adalimumab, or tocilizumab provides comparable efficacy in MTX-naïve early RA patients. Despite the limitations of indirect comparisons between trials, these studies also provided some additional evidence of comparable efficacy of abatacept and TNFi in early, MTX-naïve RA population.

2.5. Clinical safety

Introduction

Abatacept has been studied in patients with active rheumatoid arthritis in placebo controlled clinical trials (2,111 patients with abatacept, 1,099 with placebo).The safety profile of abatacept is established and 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. Pharmacovigilance activities aimed to further characterize the safety profile, as well as additional risk minimisation measure (Patient alert card) are in place from previous procedures.

In placebo controlled clinical trials with abatacept, adverse reactions (ARs) were reported in 51.8% of abatacept treated patients and 46.4% of placebo treated patients. The most frequently reported adverse reactions (≥ 5%) among abatacept treated patients were headache, nausea, and upper respiratory tract infections. The proportion of patients who discontinued treatment due to ARs was 3.3% for abatacept treated patients and 2.0% for placebo treated patients.

The first study conducted with abatacept in RA patients not previously treated with methotrexate was IM101023, using the IV formulation of abatacept. Over the 24-month study, 509 subjects received either combination therapy or MTX monotherapy for 12 months, followed by a 12-month open-label period. The results of study IM101023 were previously submitted and assessed in 2010 (EMA/H/C/00701/II/0033). Key efficacy and safety results from this study have been included in the EU Summary of Product Characteristics for Orencia (Study VI).

Data supporting this extension of indication application are mainly from Study IM101226.

Data from the three phases of the study (Treatment Period, Withdrawal Period and Re-exposure Period) are presented separately.

Patient exposure

During the Treatment Period, 119 subjects received abatacept + MTX, 116 subjects received abatacept monotherapy, and 116 subjects received MTX monotherapy.

The Withdrawal Period included 225 subjects (84 in the abatacept + MTX group, 66 in the abatacept monotherapy group and 75 in the MTX monotherapy group).

During the Re-exposure period, 55, 48, and 43 subjects in each group, respectively, were treated with abatacept + MTX. The overall mean duration of exposure to SC abatacept during the Re-treatment Period was 7 months and similar in all groups. Subjects received a mean of 20.6 injections during this period.

The overall Immunogenicity analysis population included 224 subjects treated with abatacept SC who had at least 1 immunogenicity sample taken during the study period (116 in the abatacept + MTX group and 108 in the abatacept monotherapy group).

Extent of exposure to all study medications during Treatment Period and Re-exposure Period in all treated subjects is presented in **Table 16**.

Table 16. Extent of exposure to all study medications during Treatment Period and Re-exposure Period in study IM101023

Months of Exposure	Number (%) of Subjects Abatacept + MTX N = 119	 Abatacept N = 116	 MTX N = 116
Treatment Period			
Subcutaneous Study Medication			
< 3	3 (2.5)	5 (4.3)	5 (4.3)
3- < 6	5 (4.2)	6 (5.2)	6 (5.2)
6- < 9	4 (3.4)	4 (3.4)	8 (6.9)
9- < 12	6 (5.0)	6 (5.2)	4 (3.4)
>= 12	101 (84.9)	95 (81.9)	93 (80.2)
MEAN MONTHS OF EXPOSURE[b] (SD)	12.7 (2.73)	12.4 (3.25)	12.3 (3.29)
MEDIAN (RANGE)	13.8 (2, 14)	13.8 (2, 14)	13.8 (2, 14)
Tablet Study Medication[c]			
< 3	5 (4.2)	9 (7.8)	8 (6.9)
3- < 6	6 (5.0)	4 (3.4)	8 (6.9)
6- < 9	5 (4.2)	3 (2.6)	4 (3.4)
9- < 12	20 (16.8)	31 (26.7)	27 (23.3)
>= 12	83 (69.7)	69 (59.5)	69 (59.5)
MEAN MONTHS OF EXPOSURE[d] (SD)	11.5 (3.04)	11.1 (3.59)	11.4 (4.32)
MEDIAN (RANGE)	12.6 (1, 16)	12.2 (0, 21)	12.4 (0, 27)
Re-exposure Period			
Abatacept + MTX Combination During Re-exposure Period			
<3	2 (3.6)	1 (2.1)	1 (2.3)
3 - <6	4 (7.3)	6 (12.5)	3 (7.0)
≥6	49 (89.1)	41 (85.4)	39 (90.7)
MEAN MONTHS OF EXPOSURE[e] (SD)	6.8 (1.25)	6.8 (1.29)	7.1 (1.25)
MEDIAN (RANGE)	7.3 (2, 8)	7.3 (3, 8)	7.3 (2, 11)

Adverse events

Across the entire study period, 299 of 351 subjects (85.2%) had at least 1 AE. The most common AEs across the full study period were Infections and Infestations, most commonly nasopharyngitis, upper respiratory tract infection, and urinary tract infection.

Adverse Events During Treatment Period

The overall frequency of AEs reported during the Treatment Period up to 56 days after the last dose of active drug was similar for the abatacept + MTX (85%), abatacept monotherapy (80%), and MTX monotherapy (83%) groups (**Tables 17** and **18)**.

Table 17. Overall Summary of Adverse Events Reported During Treatment Period in study IM101023- All Treated Subjects

	Number (%) of Subjects Abatacept + MTX N = 119	 Abatacept N = 116	 MTX N = 116
DEATHS	0	0	2 (1.7)
SAEs	8 (6.7)	14 (12.1)	9 (7.8)
RELATED SAEs	3 (2.5)	3 (2.6)	1 (0.9)
DISCONTINUED DUE TO SAEs	2 (1.7)	5 (4.3)	3 (2.6)
AEs	101 (84.9)	93 (80.2)	96 (82.8)
RELATED AEs	53 (44.5)	48 (41.4)	51 (44.0)
DISCONTINUED DUE TO AEs	4 (3.4)	8 (6.9)	5 (4.3)

Table 18. AEs reported during Treatment Period in study IM101023- All Treated Subjects

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116
TOTAL SUBJECTS WITH AE	101 (84.9)	93 (80.2)	96 (82.8)
INFECTIONS AND INFESTATIONS	68 (57.1)	64 (55.2)	69 (59.5)
NASOPHARYNGITIS	26 (21.8)	20 (17.2)	20 (17.2)
URINARY TRACT INFECTION	13 (10.9)	12 (10.3)	10 (8.6)
UPPER RESPIRATORY TRACT INFECTION	11 (9.2)	15 (12.9)	17 (14.7)
BRONCHITIS	8 (6.7)	5 (4.3)	8 (6.9)
SINUSITIS	8 (6.7)	4 (3.4)	2 (1.7)
GASTROENTERITIS	5 (4.2)	3 (2.6)	6 (5.2)
INFLUENZA	4 (3.4)	5 (4.3)	6 (5.2)
CYSTITIS	3 (2.5)	1 (0.9)	1 (0.9)
ORAL HERPES	3 (2.5)	0	4 (3.4)
EAR INFECTION	2 (1.7)	0	0
EYE INFECTION	2 (1.7)	0	0
FUNGAL INFECTION	2 (1.7)	0	1 (0.9)
GASTROENTERITIS VIRAL	2 (1.7)	1 (0.9)	0
HORDEOLUM	2 (1.7)	0	0
OTITIS MEDIA	2 (1.7)	0	1 (0.9)
PHARYNGITIS	2 (1.7)	6 (5.2)	6 (5.2)
PHARYNGOTONSILLITIS	2 (1.7)	2 (1.7)	1 (0.9)
PNEUMONIA	2 (1.7)	1 (0.9)	1 (0.9)
TONSILLITIS	2 (1.7)	0	0
ACUTE SINUSITIS	1 (0.8)	0	1 (0.9)
FUNGAL SKIN INFECTION	1 (0.8)	0	0
HERPES SIMPLEX	1 (0.8)	0	0

Similarly, the incidence rate of AEs was comparable across the 3 treatment groups for Months 0 to 6 of the Treatment Period (355.1, 349.5, and 400.0 per 100 p-y for the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups, respectively) and for Months 6 to 12 of the Treatment Period (178.4, 142.1, and 166.5 per 100 p-y, respectively)

The most frequently reported AEs (≥ 5% of subjects in any treatment group) during the Treatment Period are summarised in **Table 19** (frequency rates) and **Table 20** (incidence rates).

Table 19. The most frequently reported AEs (≥ 5% of subjects in any treatment group) during the Treatment Period

PREFERRED TERM (PT) (%)	Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116
TOTAL SUBJECTS WITH AE	101 (84.9)	93 (80.2)	96 (82.8)
NASOPHARYNGITIS	26 (21.8)	20 (17.2)	20 (17.2)
NAUSEA	18 (15.1)	7 (6.0)	14 (12.1)
URINARY TRACT INFECTION	13 (10.9)	12 (10.3)	10 (8.6)
UPPER RESPIRATORY TRACT INFECTION	11 (9.2)	15 (12.9)	17 (14.7)
BRONCHITIS	8 (6.7)	5 (4.3)	8 (6.9)
SINUSITIS	8 (6.7)	4 (3.4)	2 (1.7)
HEADACHE	6 (5.0)	7 (6.0)	6 (5.2)
MOUTH ULCERATION	6 (5.0)	4 (3.4)	2 (1.7)
VOMITING	6 (5.0)	2 (1.7)	0
GASTROENTERITIS	5 (4.2)	3 (2.6)	6 (5.2)
DIARRHOEA	4 (3.4)	6 (5.2)	4 (3.4)
GASTRITIS	4 (3.4)	1 (0.9)	8 (6.9)
INFLUENZA	4 (3.4)	5 (4.3)	6 (5.2)
ABDOMINAL PAIN UPPER	3 (2.5)	5 (4.3)	6 (5.2)
COUGH	3 (2.5)	7 (6.0)	6 (5.2)
PHARYNGITIS	2 (1.7)	6 (5.2)	6 (5.2)
RASH	2 (1.7)	2 (1.7)	6 (5.2)

Table 20. Exposure Adjusted Adverse Event (Occurring in at Least 5% of Treated Subjects in any Treatment Group) Summary

System Organ Class Preferred Term	Abatacept + MTX (N = 119) (P-Y = 134.7) Event Count	Rate: (IR/100 P-Y)	Abatacept (N = 116) (P-Y = 124.5) Event Count	Rate: (IR/100 P-Y)	MTX (N = 116) (P-Y = 127.7) Event Count	Rate: (IR/100 P-Y)
TOTAL EVENTS	167	124.0	135	108.4	149	116.7
INFECTIONS AND INFESTATIONS	102	75.7	91	73.1	93	72.8
NASOPHARYNGITIS	37	27.5	32	25.7	26	20.4
URINARY TRACT INFECTION	19	14.1	12	9.6	11	8.6
UPPER RESPIRATORY TRACT INFECTION	15	11.1	23	18.5	21	16.4
SINUSITIS	9	6.7	4	3.2	3	2.3
BRONCHITIS	8	5.9	5	4.0	10	7.8
GASTROENTERITIS	5	3.7	3	2.4	8	6.3
PHARYNGITIS	5	3.7	6	4.8	7	5.5
INFLUENZA	4	3.0	6	4.8	7	5.5
GASTROINTESTINAL DISORDERS	51	37.9	25	20.1	38	29.8
NAUSEA	24	17.8	7	5.6	14	11.0
MOUTH ULCERATION	9	6.7	4	3.2	2	1.6
VOMITING	6	4.5	2	1.6	0	
DIARRHOEA	5	3.7	6	4.8	4	3.1
GASTRITIS	4	3.0	1	0.8	8	6.3
ABDOMINAL PAIN UPPER	3	2.2	5	4.0	10	7.8
NERVOUS SYSTEM DISORDERS	8	5.9	7	5.6	6	4.7
HEADACHE	8	5.9	7	5.6	6	4.7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3	2.2	9	7.2	6	4.7
COUGH	3	2.2	9	7.2	6	4.7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3	2.2	3	2.4	6	4.7
RASH	3	2.2	3	2.4	6	4.7

In all treatment groups, most of the reported AEs in the Treatment Period were assessed by the investigators as mild or moderate in severity. Severe AEs were reported for 7 subjects (6%) in the abatacept + MTX group, 11 subjects (10%) in the abatacept monotherapy group, and 4 subjects (3%) in the MTX monotherapy group. No AE was assessed as very severe in intensity during the Treatment Period.

The overall frequency of AEs reported during the Treatment Period that were assessed as related to study drug was similar for the abatacept + MTX (45%), abatacept monotherapy (41%), and MTX monotherapy (44%) groups.

Severe, related AEs during the Treatment Period were: overdose in 2 subjects, and toxicity to various agents, nausea, mucosal inflammation, headache, and pancytopenia in 1 subject each in the abatacept+ MTX group, myocarditis post infection and gamma glutamyltransferase increased in the abatacept monotherapy group, and dry mouth and epistaxis in the MTX group.

Adverse events during withdrawal period

Among the 225 subjects who entered the Withdrawal Period, 46 subjects (20.4%) had at least 1 AE during the Withdrawal Period. The overall incidence rate for AEs during the entire Withdrawal Period was 25.5/100 p-y.

None of the AEs reported during the Withdrawal Period had a frequency of≥5%.

Adverse events during the re-exposure period

Among the 146 subjects who entered the Re-exposure Period, 59 subjects (40.4%) had at least 1 AE. The overall incidence rate for AEs during the entire Re-exposure Period was 37.3/100 p-y. Consistent with the AE profile during the Treatment Period, the most commonly reported events during the Re-exposure Period were infections and infestations, primarily, urinary tract infection, nasopharyngitis, and upper respiratory tract infection. Among the AEs reported during the Re-exposure Period, only urinary tract infection (5.5% of subjects) had a total frequency of ≥5%.

Serious adverse event / deaths / other significant events

Serious Adverse Events

Across the full study period, 11 subjects (9.2%), 15 subjects (12.9%), and 15 subjects (12.9%) in the abatacept + MTX group, the MTX monotherapy group, and the MTX monotherapy groups, respectively, had at least 1 SAE (**Table 21**). Most of the SAEs occurred during the Treatment Period.

Table 21. Serious Adverse events reported during full study Period in study IM101023- All Treated Subjects

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116
TOTAL SUBJECTS WITH SAE	11 (9.2)	15 (12.9)	15 (12.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5 (4.2)	2 (1.7)	2 (1.7)
OVERDOSE	3 (2.5)	1 (0.9)	2 (1.7)
POST PROCEDURAL COMPLICATION	1 (0.8)	0	0
TENDON RUPTURE	1 (0.8)	0	0
HAND FRACTURE	0	1 (0.9)	0
HEPATOBILIARY DISORDERS	2 (1.7)	0	2 (1.7)
CHOLANGITIS	1 (0.8)	0	0
CHOLECYSTITIS	1 (0.8)	0	1 (0.9)
CHOLELITHIASIS	0	0	1 (0.9)
INVESTIGATIONS	2 (1.7)	0	1 (0.9)
HEPATIC ENZYME INCREASED	1 (0.8)	0	1 (0.9)
TRANSAMINASES INCREASED	1 (0.8)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (1.7)	2 (1.7)	4 (3.4)
BASAL CELL CARCINOMA	1 (0.8)	0	0
PROSTATE CANCER	1 (0.8)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) (Cont'd)			
BOWEN'S DISEASE	0	1 (0.9)	0
CARCINOID TUMOUR PULMONARY	0	1 (0.9)	0
COLON ADENOMA	0	0	1 (0.9)
INVASIVE DUCTAL BREAST CARCINOMA	0	0	1 (0.9)
UTERINE CANCER	0	0	1 (0.9)
UTERINE NEOPLASM	0	0	1 (0.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.8)	1 (0.9)	0
PANCYTOPENIA	1 (0.8)	0	0
ANAEMIA	0	1 (0.9)	0
INFECTIONS AND INFESTATIONS	1 (0.8)	4 (3.4)	1 (0.9)
PNEUMONIA	1 (0.8)	1 (0.9)	0
ABSCESS LIMB	0	1 (0.9)	0
HERPES ZOSTER	0	1 (0.9)	0
PYELONEPHRITIS	0	0	1 (0.9)
URINARY TRACT INFECTION	0	0	1 (0.9)

Serious adverse events during the treatment period

During the Treatment Period, 31 of 351 subjects (9%) had at least 1 SAE. The percentage of subjects with SAEs was higher in the abatacept monotherapy group (14 subjects [12%]) than in the abatacept + MTX group (8 subjects [7%]) and MTX monotherapy group (9 subjects [8%]).

Overdose was the only individual SAE that was reported by > 1 subject in any treatment group (i.e., 3 subjects in the abatacept + MTX group and 1 subject each in the other 2 groups). Two reports of serious overdose in the abatacept + MTX group during the Treatment Period were assessed by the investigators as related to study drug, and both were related to an overdose of oral MTX.

Related serious adverse events

Seven subjects had SAEs during the Treatment Period that were considered by the investigators to be related to the study drug (3 each in the abatacept + MTX and abatacept monotherapy groups and 1 in the MTX monotherapy group). For 5 subjects, the related SAEs led to discontinuation of study drugs during the Treatment Period. All related SAEs resolved either following discontinuation from the study and/or therapeutic intervention:

• Abatacept + MTX group - pancytopenia/increased hepatic enzymes in 1 subject and MTX overdose in 2 subjects

• Abatacept monotherapy group - Bowen's disease, myocarditis post infection, and herpes zoster infection in 1 subject each

• MTX monotherapy group - increased hepatic enzymes in 1 subject.

Serious adverse events during the withdrawal period

Seven of 225 subjects (3.1%) who entered the Withdrawal Period had a SAE with an onset > 56days after the last dose of active drug in the Treatment Period up to the start of the Re-exposure Period (2 subjects in the abatacept + MTX group and 5 subjects in the MTX monotherapy group). None of the SAEs were considered by the investigators to be related to the study drug. One of these SAEs (uterine neoplasm) in the MTX monotherapy group resulted in discontinuation from the study and subsequently, death. Other than this event, none of the SAEs reported during the Withdrawal Period led to discontinuation from the study, and all but 2 SAEs (post-procedure complication of hepatopathy following cholecystectomy and prostate cancer) had resolved prior to database lock

Serious adverse events during the re-exposure period

Four of 146 subjects who entered the Re-exposure Period had had an SAE. One of the SAEs (abatacept overdose) was considered by the investigators to be related to the study drug.

Other significant adverse events

In the following sections, AEs of special interest have been prospectively identified to be those that may be associated with the use of immunomodulatory agents. They are a subset of all AEs and may be either serious or non-serious.

Infections

Treatment Period

A similar percentage of subjects in each treatment group had an infection up to 56 days after the last dose of active drug in the Treatment Period: 57%, 55%, and 60% in the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups, respectively.

Nasopharyngitis was the most frequently reported infection in all 3 treatment groups, reported for 17% to 22% of subjects across the 3 groups. All reported infection and infestation AEs during the Treatment Period were mild or moderate in severity, except for 3 events in 2 subjects the abatacept monotherapy group (viral infection, abscess limb and furuncle).

During the Treatment Period, the incidence rate of infections was similar for the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups during both Months 0 to 6 (116.6, 126.1, and 110.7 per 100 p-y, respectively). From Months 6 to 12, the incidence rate of infections decreased (64.6, 66.5, and 72.8 per 100 p-y, respectively).

Serious infections during the Treatment Period were reported for 1 subject in the abatacept + MTX group (pneumonia) and in 4 subjects (3%) in the abatacept monotherapy group (pneumonia, abscess limb, herpes zoster, viral infection). With the exception of the serious herpes zoster infection, none of the serious

infections during the Treatment Period was assessed as related to study drug.

Only a single infection-related AE led to discontinuation during the Treatment Period; this event (herpes zoster in abatacept monotherapy group) was serious.

Withdrawal Period

Twenty-four of 225 subjects (11%) who entered the Withdrawal Period had infections reported with an onset > 56 days after the last dose of active drug in the Treatment Period up to the start of the Re-exposure Period. These subjects were distributed across the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups (n = 8 [10%], n = 6 [9%], and n = 10 [13%], respectively).

The overall incidence of infections during the Withdrawal Period was 8.1 per 100 person years (6.5, 5.4, and 12.2 per 100 person years for the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups, respectively) (Table S.6.41).

Overall, the most common infections during the Withdrawal Period were nasopharyngitis, upper respiratory tract infection, urinary tract infection (2.2% each), and gastroenteritis (1.3%). All other infections during the Withdrawal Period were reported for <1% of subjects. Upper respiratory tract infection and nasopharyngitis (2% each) were the only related infections reported in > 1% of subjects during the Withdrawal Period.

All infections were mild or moderate in intensity with the exception of 1 event of pyelonephritis in a subject in the MTX monotherapy group. This event was also serious.

A serious event of urinary tract infection was also reported during the Withdrawal Period. No subject discontinued from the study due to an infection during the Withdrawal Period.

Re-exposure Period

A total of 37 of 146 subjects (25.3%) who entered the Re-exposure Period had infections during the Re-exposure Period. The overall incidence of infections during the Re-exposure Period was 16.1/100 p-y. Overall, the most common infections during the Re-exposure Period were urinary tract infection (5.5%), nasopharyngitis (4.8%), upper respiratory tract infection (3.4%), and bronchitis, conjunctivitis, folliculitis, influenza, and pharyngitis (1.4% each). All other infections during the Re-exposure Period were reported for < 1% of subjects.

All infections were mild or moderate in intensity with the exception of 1 event of bronchitis. No subject was discontinued from the study due to an infection during the Re-exposure Period.

Malignancies

Treatment Period

Four malignancies were reported during the Treatment Period, 1 in the abatacept + MTX group (basal cell carcinoma), 2 in the abatacept monotherapy group (Bowen's disease and pulmonary carcinoid tumour), and 1 in the MTX monotherapy group (invasive ductal breast carcinoma).

All malignancies were reported as SAEs; the event of Bowen's disease was considered by the investigator to be related to the study drug.

During the Treatment Period, the incidence rate for malignancies was 1.8 per 100 person years for the abatacept monotherapy and MTX monotherapy groups during Months 0 to 6 and was 1.0 per 100 person years each for the abatacept + MTX and abatacept monotherapy groups during Months 6 to 12.

Withdrawal Period

Two subjects who entered the Withdrawal Period had a malignancy with an onset > 56 days after the last

dose of active drug in the Treatment Period up to the start of the Re-exposure Period. The overall incidence of malignancies during the Withdrawal Period was 0.8 per 100 person years.

One subject in the MTX monotherapy group had a uterine neoplasm that resulted in death. This malignancy occurred during the first 6 months of the Withdrawal Period (Months 12 to 18).

One subject in the abatacept + MTX group had a benign keratoacanthoma on the left ear and prostate cancer. Both events occurred during the second 6 months of the Withdrawal Period (i.e., > Month 18). These malignancies were not considered by the investigators to be related to the study drug.

Re-exposure Period

No subject had an event of malignancy during the Re-exposure Period.

Post-study Period

Two malignancies were reported during the post-study period (i.e., > 56 days after the subject was withdrawn from the study). Uterine cancer was reported in 1 subject in the MTX monotherapy group and lung adenocarcinoma was reported in 1 subject in the abatacept + MTX group.

Autoimmune Disorders

Treatment Period

Six subjects had pre-specified autoimmune disorder AEs during the Treatment Period (1 subject in the abatacept + MTX group, 2 subjects in the abatacept monotherapy group, and 3 subjects in the MTX monotherapy group.

The incidence rate for pre-specified autoimmune disorders was 1.8 per 100 person years and 3.6 per 100 person years for the abatacept monotherapy and MTX monotherapy groups, respectively, during Months 0 to 6, and was 2.0 per 100 person years for the abatacept monotherapy group and 1.0 per 100 person years each for the abatacept + MTX and MTX monotherapy groups during Months 6 to 12.

The autoimmune disorders reported during the Treatment Period among abatacept-exposed subjects were mild Raynaud's phenomenon in the abatacept + MTX group, and moderate Sjögren's syndrome and moderate psoriasis in the abatacept monotherapy group.

The latter event was the only autoimmune disorder reported during the Treatment Period that was assessed as related to study drug. None of the reported autoimmune disorder events was serious and none resulted in discontinuation of study drug.

Withdrawal Period

One subject in the MTX group had an autoimmune disorder (pre-specified) of scleritis during the Withdrawal Period. The event was considered severe in intensity and not related to study drug.

Re-exposure Period

No autoimmune disorders (pre-specified) were reported during the Re-exposure Period.

Local Injection Site Reactions (Pre-specified)

During the Treatment Period, 3 pre-specified local injection site reactions were reported for 2 subjects in the abatacept + MTX group only (mild injection site swelling). These events were non-serious and all resolved within 1 day while the subjects remained in the study.

The incidence rate for these events was 2.9 per 100 person years for the abatacept + MTX group during Months 6 to 12; no local injection site reactions were reported during Months 0 to 6 of the Treatment Period.

No local injection site reactions (pre-specified) occurred during the Re-exposure Period.

Deaths

Two deaths occurred during the study (both in the MTX monotherapy group and both after discontinuation from the Withdrawal Period). One subject underwent total abdominal hysterectomy because of uterine cancer on Day471. Uterine cancer event was thought to be resolved. On Day 475 the subject died due to respiratory failure.

Another subject died on Day 470 due to uterine neoplasm and renal failure.

Laboratory findings

During the Treatment Period, the frequencies of hematologic and blood chemistry parameters that met the sponsor-defined criteria for a marked abnormality, was small (typically < 5%), and generally similar across the 3 treatment groups.

Marked abnormalities in hematology and clinical chemistry parameters were also infrequently reported during the Withdrawal Period, with the most frequent abnormalities consisting of abnormalities in serum glucose (9% of total subjects with marked reduction, and 2% of total subjects with marked elevation).

Marked abnormalities in hematology and clinical chemistry parameters were infrequent during the Re exposure Period and were consistent with the incidence observed during the Treatment Period.

Safety in special populations

There were only 3 subjects whose ages were 75 years or over in the TP and no subjects 85 years or older. 26 subjects (7.4%) were in the 65-74 years subgroup. No unexpected AEs were reported in the elderly subpopulations.

Exposure during pregnancy

Five pregnancies were reported among the study participants. For 3 subjects, the pregnancy resulted in discontinuation of study treatment. In two cases, no information was avaialble on the outcome of the preganacy. In the other three cases, the outcome was reported as delivery of healthy, full-term infants.

Immunological events

The abatacept-associated immunogenicity rates at each assessment time during the treatment, withdrawal, and re-exposure periods are summarized by treatment group and type of seropositive response (CTLA4 and possibly Ig or Ig and/or junction region, and combined) in **Table 22**.

Table 22. Proportion of subjects with positive abatacept-induced responses (ECL Method) Over Time During Study Period - Immunogenicity Population

As Treated Treatment Group	Study Day	CTLA4 AND POSSIBLY IG n/N (%)	IG AND/OR JUNCTION REGION n/N (%)	Total n/N (%)
SC ABA + MTX	TP Day 365	3 /103 (2.9%)	0 /103 (0.0%)	3 /103 (2.9%)
	WP Day 365	27 / 77 (35.1%)	2 / 77 (2.6%)	29 / 77 (37.7%)
	RP Day 85	2 / 49 (4.1%)	3 / 49 (6.1%)	5 / 49 (10.2%)
	RP Day 169	2 / 44 (4.5%)	2 / 44 (4.5%)	4 / 44 (9.1%)
	Overall on Re-exposure Visits	3 / 53 (5.7%)	5 / 53 (9.4%)	7 / 53 (13.2%)
	28 Days Post	9 / 70 (12.9%)	3 / 70 (4.3%)	12 / 70 (17.1%)
	85 Days Post	13 / 65 (20.0%)	3 / 65 (4.6%)	16 / 65 (24.6%)
	168 Days Post	20 / 62 (32.3%)	2 / 62 (3.2%)	22 / 62 (35.5%)
	Overall Post Visits	33 / 84 (39.3%)	6 / 84 (7.1%)	36 / 84 (42.9%)
	Overall	49 /116 (42.2%)	8 /116 (6.9%)	52 /116 (44.8%)
SC ABA	TP Day 365	2 /101 (2.0%)	3 /101 (3.0%)	5 /101 (5.0%)
	WP Day 365	22 / 59 (37.3%)	4 / 59 (6.8%)	26 / 59 (44.1%)
	RP Day 85	4 / 43 (9.3%)	1 / 43 (2.3%)	5 / 43 (11.6%)
	RP Day 169	1 / 40 (2.5%)	1 / 40 (2.5%)	2 / 40 (5.0%)
	Overall on Re-exposure Visits	4 / 45 (8.9%)	2 / 45 (4.4%)	6 / 45 (13.3%)
	28 Days Post	7 / 65 (10.8%)	1 / 65 (1.5%)	8 / 65 (12.3%)
	85 Days Post	14 / 65 (21.5%)	2 / 65 (3.1%)	16 / 65 (24.6%)
	168 Days Post	17 / 67 (25.4%)	5 / 67 (7.5%)	21 / 67 (31.3%)
	Overall Post Visits	23 / 80 (28.8%)	6 / 80 (7.5%)	27 / 80 (33.8%)
	Overall	39 /108 (36.1%)	10 /108 (9.3%)	47 /108 (43.5%)

At TP Day 365, the combined immunogenicity rates were 2.9% and 5% in the abatacept + MTX and abatacept monotherapy group, respectively. These low rates and low titers during the treatment period were consistent with rates previously observed in the abatacept SC program.

During the Withdrawal Period, 29 of 77 subjects (37.7%) in the abatacept + MTX group and 26 of 59 subjects (44.1%) in the abatacept monotherapy group with samples assessed had positive responses to CTLA4 and possibly Ig or IG and/or junction region. In the Re-exposure Period, 7 of 53 subjects (13.2%) in the abatacept + MTX group and 6 of 45 subjects (13.3%) in the abatacept monotherapy group had positive responses.

For most subjects with abatacept-induced seropositive CLTLA4 and possibly Ig responses, titers were low (< 100); only 6 subjects had CTLA4 and possibly Ig titers of > 200. For many subjects, abatacept-induced seropositivity was observed at only a single time point and was followed by at least 1 sample that was negative for anti-abatacept antibodies.

Discontinuation due to adverse events

Across the full study period, 3.4%, 6.9%, and 6.0% of subjects in the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups, respectively, had an AE that led to discontinuation from the study.

During the Treatment Period, 17 subjects (5%) had AEs leading to the discontinuation of study drug. The percentage of subjects who had AEs leading to the discontinuation of study drug was similar across the 3 groups (4 subjects [3%] in the abatacept + MTX group, 8 subjects [7%] in the abatacept monotherapy group, and 5 subjects [4%] in the MTX group).

Overall, overdose was the most common AE leading to discontinuation (1 subject in each treatment group), and each of these 3 events was considered serious. No other individual AE leading to discontinuation of study therapy occurred in > 1 subject across the 3 treatment groups. All AEs leading to discontinuation during the Treatment Period in the abatacept + MTX group resolved. All but 1 AE leading to discontinuation in the

abatacept monotherapy group (emphysema) and 2 AEs leading to discontinuation in the MTX monotherapy group (hypertension and invasive ductal breast carcinoma) resolved by the cut-off date.

Two of 225 subjects (1%) (both in the MTX monotherapy group) who entered the Withdrawal Period discontinued study drug due to an AE. The AEs leading to discontinuation were uterine neoplasm (subsequently resulting in death) and nausea in 1 subject each. Neither AE occurred within the first 6 months of the Withdrawal Period (i.e., Months 12 to 18).

No subjects in the Re-exposure group had AEs leading to the discontinuation of study drug.

Comparison of safety data from AGREE and AVERT studies

Table 23. Key Baseline Demographic and Disease Characteristics - AVERT (ITT Population) and AGREE (All Randomized and Treated Subjects)

Baseline Characteristic	AVERT N = 351	AGREE N = 509
Age, y (mean ±SD)	47.0 ±12.6	49.9 ±12.7
Gender, female (n [%])	273 (77.8%)	395 (77.6%)
Race, White (n [%])	124 (84.9%)	421 (82.7%)
Duration of RA, y (mean ±SD)[a]	0.56 ±0.50	0.54 ±0.61
DAS28-CRP score (mean ±SD)	5.4 ±1.2	6.3 ±1.0
Swollen joints (mean number)	16.5 ±12.4	22.4 ±10.8
Tender joints (mean number)	23.3 ±14.8	31.0 ±14.4
HAQ DI scores (mean ±SD])	1.42 ±0.66	1.7 ±0.7
CRP level, mg/mL (AVERT); mg/dL (AGREE) (mean ±SD)	17.5 ±24.99	3.4 ±4.2
RF status positive (n [%])[b]	334 (95.2)	491 (96.5)

Abbreviations: DAS28-CRP = Disease Activity Score 28 based on C-reactive protein; HAQ-DI = Health Activities Questionnaire - Disability Index; RA = rheumatoid arthritis, RF = rheumatoid factor, SD = standard deviation.
[a]Duration of RA in AGREE CSR reported in months, conversion factor: months/12 = years.

[b]Per Inclusion Criteria, subjects were required to be ACPA positive at baseline; 4 subjects were not ACPA positive, and these cases were considered protocol deviations.

Notes: Baseline is Day 1 of the study. Two additional subjects qualified for inclusion in the analysis population for the Withdrawal Period in the long-term (2-year) analysis.
- Overall mean for tender and swollen joints were based on 68-total scoring system.
- ACPA positive status was required by inclusion criteria; 4 subjects in AVERT did not have ACPA+ status at baseline.

Analysis of Adverse Events

No new safety signals were evident in either study during the long-term use of abatacept in combination with MTX for up to 18 months of treatment in study IM101226 (Treatment and Re-exposure Periods) and up to 24 months in study IM101023 (Blind plus Open-label Periods). The types of AEs observed were similar across periods for both studies.

The overall AE summaries for both studies are presented in **Table 24**.

Table 24. Overall summary of adverse events reported during treatment period in IMI010226 and during the blinded period pf treatment in IMI01023-All treated subjects

	Number (%) of Subjects				
	IM1010226[a]			IM1010023[b]	
	Abatacept + MTX N = 119	Abatacept N = 116	MTX N = 116	Abatacept + MTX N = 256	Placebo + MTX N = 253
DEATHS	0	0	2 (1.7)	2 (0.8)	4 (1.6)
SAEs	8 (6.7)	14 (12.1)	9 (7.8)	20 (7.8)	20 (7.9)
RELATED SAEs	3 (2.5)	3 (2.6)	1 (0.9)	5 (2.0)	6 (2.4)
DISCONTINUED DUE TO SAEs	2 (1.7)	5 (4.3)	3 (2.6)	3 (1.2)	3 (1.2)
AEs	101 (84.9)	93 (80.2)	96 (82.8)	217 (84.8)	211 83.4)
RELATED AEs	53 (44.5)	48 (41.4)	51 (44.0)	98 (38.3)	114 (45.1)
DISCONTINUED DUE TO AEs	4 (3.4)	8 (6.9)	5 (4.3)	8 (3.1)	11 (4.3)

[a] Includes data up to 56 days post the last dosing day (active abatacept or active MTX, whichever is the later). Includes all deaths reported during Study Period including those that occurred > 56 days after last dose in Treatment Period. Related AE or SAE defined as AE or SAE with Certain, Probable, Possible, or Missing relationship to study medication. MEDDRA VERSION: 10.1
[b] Includes data up to 56 days post the 1st year of treatment or start of the 2nd year, whichever occurred first. Related AE or SAE defined as Certain, Probable, Possible, or Missing. MEDDRA VERSION: 16.1
Note: SAEs include hospitalizations for elective surgical procedures

Deaths

Study IM101226

Two deaths occurred during the study (both in the MTX monotherapy group during the Withdrawal Period). Neither death was considered by the investigator to be related to study treatment (Table 3.2-1). One subject died on Day 475 due to respiratory failure after hysterectomy by reason of uterine cancer and 1 subject died on Day 470 due to uterine neoplasm and renal failure.

Study IM101023

Deaths were reported in 2 subjects (0.8%) in the abatacept + MTX group and 4 subjects (1.6%) in the placebo + MTX group in the first 12 months of the study (Table 3.2-2). The deaths in the abatacept + MTX group were considered by the investigator as probably related to study drug. Two (2) of the subjects who died in the placebo + MTX group were reported to have discontinued due to an AE.

In the open-label period, there were 2 deaths (1 in the original abatacept + MTX group; 1 in the original placebo + MTX group; Table 3.2-2). These 2 deaths were the result of SAEs reported in the open-label period that were considered possibly related to study drug by the investigator (pneumonia, and pneumonia with septic shock).

Other Serious Adverse Events

All reported SAEs are summarised for studies IM101226 and IM101023 in **Tables 25, 26** and **27.**

Table 25. Serious adverse events reported during treatment period in IMI010226 and during the blinded period of treatment in IMI01023-All treated subjects

	Number (%) of subjects				
	IM101226			IM101023	
	Abatacept + MTX	Abatacept	MTX	Abatacept + MTX	Placebo + MTX
N	119	116	116	256	253
All SAEs	8 (6.7)	14 (12.1)	9 (7.8)	20 (7.8)	20 (7.9)
Related SAEs	3 (2.5)	3 (2.6)	1 (0.9)	5 (2.0)	6 (2.4)
SAEs reported by > 1 subject	3 (2.5)[a]				3 (1.2)[b]

Includes data up to 56 days post the 1st year of treatment or start of the 2nd year, whichever occurred first.

Table 26. Serious adverse events reported during the withdrawal and the re-exposure periods in IMI010226 –All subjects entering the withdrawal period or the re-exposure period

	Number (%) of subjects		
	IM101226		
	Abatacept + MTX	Abatacept	MTX
Withdrawal Period (IM101226)			
N	84	66	75
All SAEs	2 (2.4)	0	5 (6.7)
Related SAEs			
Re-exposure Period (IM101226)			
N	55	48	43
All SAEs	2 (3.6)	1 (2.1)	1 (2.3)
Related SAEs[a]	0	0	1 (2.3)

Includes data up to 56 days post the 1st year of treatment or start of the 2nd year, whichever occurred first.

Table 27. Serious adverse events reported during open-label period in IMI010223 and during the blinded period in IMI01023-All treated subjects

	Number (%) of subjects
	Abatacept + MTX
N	459
All SAEs	29 (6.3)
Related SAEs[a]	10 (2.2)

Includes data up to 56 days post the 1st year of treatment or start of the 2nd year, whichever occurred first.
MEDDRA VERSION: 11.1.

[a]Pneumonia was reported in 3 subjects.

Events Leading to Discontinuation in Study IM101226

Across the full study period, 3.4%, 6.9%, and 6.0% of subjects in the abatacept + MTX, abatacept monotherapy, and MTX monotherapy groups, respectively, had an AE that led to discontinuation from the study.

Treatment Period

During the Treatment Period, 17 subjects (5%) had AEs leading to the discontinuation of study drug. The percentage of subjects who had AEs leading to the discontinuation of study drug was similar across the abatacept+MTX and MTX groups (4 subjects [3%] in the abatacept + MTX group, and 5 subjects [4%] in the MTX group). 8 subjects [7%] in the abatacept monotherapy group had AEs leading to discontinuation.

Overall, overdose was the most common AE leading to discontinuation (1 subject in each treatment group), and each of these 3 events was considered serious.

No other individual AE leading to discontinuation of study therapy occurred in> 1 subject across all 3 treatment groups.

All AEs leading to discontinuation during the Treatment Period in the abatacept + MTX group resolved.

All but 1 AE leading to discontinuation in the abatacept monotherapy group (emphysema) and 2 AEs leading to discontinuation in the MTX monotherapy group (hypertension and invasive ductal breast carcinoma) resolved by the cutoff date.

One subject in the abatacept + MTX group was discontinued from the study due to AEs (anemia and weight decreased) that had onsets prior to randomization (Day -5) and thus were not treatment emergent.

Withdrawal Period

During the Withdrawal Period, 2 of 225 subjects (1%; both in the MTX monotherapy group) discontinued study drug due to an AE**.** AEs leading to discontinuation were uterine neoplasm (subsequently resulting in death) and nausea in 1 subject each (both occurring after Month 18).

Re-exposure Period

No subjects in the Re-exposure group had AEs leading to the discontinuation of study drug.

Events Leading to Discontinuation in Study IM101023

Blinded Period (First Year)

The proportion of subjects who discontinued due to an AE was low in both treatment groups (abatacept + MTX: 3.1%; placebo + MTX: 4.3%). A small number of subjects in each group were discontinued from the study due to a SAE (1.2% of subjects each in the abatacept + MTX and placebo + MTX groups)

Open-label Period (Second Year)

In the open-label period, 11 (2.4%) subjects (4 in the original abatacept + MTX group; 7 in the original placebo + MTX group) discontinued treatment due to an AE or multiple AEs. 4 of these subjects had AE(s) that were considered serious and 5 of these subjects had AEs that were considered related to study therapy.

There was no pattern in the AEs that led to discontinuation; no individual AE resulted in the discontinuation of more than 1 subject.

Two of these subjects died as a result of the AE.

Post marketing experience

To assess the safety of abatacept prescribed as first line therapy using real world data, the MAH analysed two US data sources, (as abatacept is approved as first line therapy for the treatment of RA in the US) with the objective of comparing the risk of pre-specified events among patients initiating abatacept and TNFi as the first line biologic. The data sources selected for these analyses included MarketScan Commercial and Supplemental Medicare (MarketScan) [Study IM101488] and the National Data Bank for Rheumatic Diseases (NDB) [Study IM101045B].

In Study IM101488, adult subjects diagnosed with RA who initiated treatment with abatacept or a TNFi between July 1, 2006 and July 31, 2012 were eligible for inclusion in the analysis. Patients were defined as having first line therapy if a claim for abatacept or a TNFi was made without having a claim for a biologic drug during the 180 day period prior to the abatacept or TNFi claim.

In Study IM101045B, adult subjects with RA who completed a comprehensive follow-up questionnaire after 2005 and who initiated treatment with abatacept or a TNFi were eligible for inclusion in the analysis. First line was defined as the initiation of abatacept or a TNFi without reported prior use of a biologic.

In Study IM101488, propensity scores were estimated by logistic regression analyses to measure potential predictors of therapy initiation, including age, gender, year of therapy initiation, and select co-morbidities and medications prescribed in the 180 days prior to treatment initiation. A Cox regression analysis, adjusted

for propensity score and unbalanced predictors (i.e., cardiovascular disease), was conducted to compare the 2 cohorts. These results were reported as *adjusted hazard ratios*.

In Study IM101045B, marginal structural models were used to estimate the effect of treatment on the outcome by an appropriate control for the effects of time-dependent confounders. Variables included sex, employment status, marital status, smoking status, education level, income, and select co-morbidities, and medications prescribed. These results were reported as *adjusted HRs*.

Baseline Characteristics

In Study IM101488, there were 5,808 patients exposed to abatacept and 28,091 patients exposed to TNFi. Patients prescribed abatacept first line were older (mean age 56.5 vs 52.7) and more likely to have had a claim for hypertension, diabetes, hospitalized infections, malignancy, chronic obstructive pulmonary disease, asthma, and chronic kidney disease in the 180 days before treatment initiation compared to patients prescribed a TNFi first line. Abatacept patients were also more likely to have been prescribed a non-biologic DMARD, IV antibiotics and corticosteroids during the 180 days before treatment initiation compared to TNFi patients.

In Study IM101045B, there were 348 patients exposed to abatacept and 2,740 patients exposed to TNFi. Patients prescribed abatacept first line were older (mean age 62.5 vs 57.9), more likely to have had a history of smoking, have had hypertension and diabetes and have used prednisone compared to patients prescribed a TNFi first line.

Hazard Ratios

The hazard ratios for the pre-specified events in both studies are summarised in **Table 28**.

Table 28. Hazard ratios for events of infections and malignancies for patients in treated with abatacept compared to TNF inhibitors- Studies IM101488 and IM101045B

	Crude HR (95% CI)	Adjusted HR(95% CI)
IM101488		
Hospitalized infections	0.9 (0.7,1.2)	0.9 (0.7, 1.2)
Opportunistic infections	1.2 (1.0,1.4)	1.2 (1.0, 1.5)
Total malignancy	1.4 (1.2, 1.6)	1.02 (0.8, 1.3)
Breast cancer	1.6 (1.1, 2.1)	1.2 (0.7, 1.9)
Lung Cancer	1.1 (0.7, 1.7)	0.4 (0.2, 0.9)
Lymphoma	1.0 (0.6,1.7)	0.9 (0.4, 2.0)
IM101045B		
Hospitalized infections	0.6 (0.2, 2.2)	0.48 (0.15, 1.5)
Opportunistic infections	NA	NA
Total malignancy	1.7 (0.9, 2.9)	1.2 (0.7, 2.0)
NMSC	2.0 (1.0, 3.9)	1.4 (0.8, 2.6)

NA = Not Applicable (number of events was too small and convergence was not achieved in the model); NMSC = non-melanoma skin cancer.

2.5.1. Discussion on clinical safety

Safety data in MTX-naive RA population from the pivotal study IM101226 (119 patients on sc abatacept + MTX, 116 on sc abatacept, 116 on MTX) and the supportive study IM101023 (256 patients on iv abatacept + MTX, 253 on MTX) were submitted in support of this application.

The use of previous IV abatacept (+MTX) data to support the safety of this combination in this larger early RA patient population not previously treated with MTX was considered appropriate, however, as the study designs differed considerably, only overall AE profiles were comparable.

The overall frequency of AEs reported during the Treatment Period in study IM101226 was similar for the abatacept + MTX (85%), abatacept monotherapy (80%), and MTX monotherapy (83%) groups. The most common AEs were nasopharyngitis, upper respiratory infections and urinary tract infections. Nausea was more common in subjects with MTX use (abatacept + MTX group, MTX group) compared to abatacept monotherapy.

The overall frequency of AEs in study IM101226 was also comparable to that reported from the study IM101023 during the first year treatment [(abatacept + MTX (85%), MTX monotherapy (83%)].

When comparison between studies was performed, the proportion of subjects with SAEs and serious infections at 1 year were also very similar:

SAEs: 7% in abatacept + MTX and 8% in MTX monotherapy (IM101226) vs. 8% abatacept + MTX and 8% in MTX monotherapy (IM101023), respectively.

Serious infections: 1% in abatacept + MTX and 1% in MTX monotherapy (IM101226) vs. 2% abatacept + MTX and 2% in MTX monotherapy (IM101023), respectively.

The frequencies of other relevant safety parameters such as the number of related AEs, and the incidence of AEs of special interest were also similar in the pivotal study and in line with previous experience of Orencia. Three subjects each in the abatacept + MTX and abatacept monotherapy groups and 1 subject in the MTX monotherapy group had SAEs during the Treatment Period that were considered related to study treatment by the investigators. All related SAEs resolved either following discontinuation from the study and/or therapeutic intervention.

No deaths were reported with abatacept at any time during the study. Two deaths were reported with MTX (respiratory failure after hysterectomy by reason of uterine cancer in 1 subject and uterine neoplasm and acute renal failure in 1 subject) during the Withdrawal Period.

A similar percentage of subjects in the abatacept + MTX and MTX monotherapy groups (3% and 4%, respectively) were discontinued from the Treatment Period due to AEs; in the abatacept monotherapy group, however, 7% of subjects were discontinued due to an AE during the Treatment Period.

The frequencies of AEs of clinical interest such as infections, malignancies, autoimmune disorders and injection-related events were also comparable between different treatment groups in the pivotal study.

Four malignancies were reported during the Treatment Period, including 1 in the abatacept + MTX group (basal cell carcinoma), 2 in the abatacept monotherapy group (Bowen's disease, carcinoid tumor pulmonary), and 1 in the MTX monotherapy group (invasive ductal breast carcinoma). Furthermore, two other malignancies occurred during the Withdrawal Period: one uterine cancer and one uterine neoplasm event, both leading to death of the subject concerned.

Pre-specified autoimmune disorder AEs were reported during the Treatment Period for 1 subject in the abatacept + MTX group, 2 subjects in the abatacept monotherapy group, and 3 subjects in the MTX monotherapy group. None of these events was a SAE or resulted in discontinuation of study drug.

Pre-specified local injection site reactions were reported for 2 subjects (2%) in the abatacept + MTX group only (mild injection site swelling). Each event was nonserious and resolved within 1 day.

Subjects with RA are thought to have a higher rate of infection than non-RA subjects (Doran et al, 2002). Literature data also suggest that subjects with increased RA disease activity have a higher rate of serious infection than subjects with lower disease activity (Emery et al, 2014), and an increased rate also for infections with increased DAS28 parameters (Favalli et al, 2009). It is also known that systemic corticosteroid use increases susceptibility to infections. With decreasing disease activity, corticosteroid dose can also be decreased, which might result in a decrease in the infection rate. Therefore it is reasonable to suggest that the observed increased risk of infections in the Treatment Period compared to Re-Exposure Period could be due to the disease itself, the level of disease activity, and the associated therapies (Emery et al, 2014).

The safety profiles of abatacept in combination with MTX in studies IM101226 and IM1010123 were consistent with previous clinical experience in MTX-IR and TNF-IR subjects, and with the known safety profile of abatacept, as characterized in the abatacept Risk Management Plan.

Safety results from study IM101226 thus confirmed those observed previously in study IM101023, and no new clinically important safety issues were identified.

The unique design of study IM101226 provides new safety information for both SC abatacept in combination with MTX and as monotherapy in subjects with early, active RA. While the abatacept monotherapy group had a numerically somewhat higher frequency of SAEs, including serious infections, these numbers are too small to suggest a clinically relevant difference.

In study IM101023, similar immunogenicity rates were seen in patients on treatment for the abatacept+ MTX, and abatacept monotherapy groups (2.9% (3/103) and 5.0% (5/101), respectively) during the double-blind 12 month period. Increased rates of immunogenicity were observed in subjects tested during 6 months of complete drug withdrawal in the abatacept + MTX and abatacept monotherapy groups (37.7% [29/77] and 44.1% [27/59], respectively) with generally low titer antibody responses. No clinical impact of these antibody responses was detected, and no safety concerns were observed upon re-initiation of abatacept therapy.

Of the 55 patients who developed ADAs, during the withdrawal period, eleven patients reported AEs, two of which were potentially immune-mediated. Both patients entered the re-treatment without further problems and achieved a treatment response.

Impact of ADAs on efficacy was reviewed by analysing the treatment responses in 8 patients with ADAs during treatment period. With the exception of one patient, all achieved a treatment response.

Impact of ADAs during re-treatment period (RP): Forty-six patients who had ADAs during the withdrawal period (WP) entered the re-treatment period. There was a significant treatment effect (DAS28-CRP). The response was numerically higher in the abatacept + methotrexate group. The treatment response and likelihood of re-gaining the original level of response were similar in the ADA-positive group and the whole RP-group. Seventeen out of 46 ADA-positive patients reported AEs during re-treatment period. Two events (severe pruritus and mild urticaria) were possibly immune-mediated but did not lead to permanent withdrawal from abatacept-treatment. No autoimmune disorders were reported.

Post-marketing data were also submitted fromt he US to assess any potential differecnes in the safety of abastacept when used as first line therapy in RA. The two studies (IM10148 and IM101045B) submitted reported on the adjusted hazard rations of various types of infections and malignancies.

In Study IM101488, the crude HR was significantly elevated in the abatacept cohort for total malignancy and breast cancer but this risk was attenuated and lost significance after adjustment for propensity score and

cardiovascular disease. The crude HR for lung cancer was also elevated in the abatacept cohort but not significantly and the risk was further attenuated after adjustment for propensity score and cardiovascular disease.

In Study IM101045B, the crude HR for abatacept was non-significantly elevated for total malignancy and NMSC and was attenuated after adjustment for multiple variables. There were no events of breast cancer or lymphoma among the abatacept treated patients so models could not be run for these outcomes.

In both studies, the crude HR for comparing patients prescribed abatacept to patients prescribed a TNFi was not statistically different for hospitalized infections.

Overall, the submitted post-marketing data were consistent with the known safety profile for abatacept from the clinical trial experience, with no new signal identified with first line use.

2.5.2. Conclusions on clinical safety

The safety profile of abatacept is well established and 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. Risk minimisation as well as pharmacovigilance activities are in place from previous procedures. Based on the data currently available, the adverse event incidence and profile of abatacept in MTX-naive RA-population appears consistent with the previous experience with abatacept. There were a slightly higher numbers of serious infections reported in the abatacept monotherapy group, but there was no consistent pattern that emerged in a specific infection or group of infections that had a larger probability to occur in the abatacept treatment group. No such increase in serious infections was seen in the combination arm relative to the MTX alone arm.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 22 December 2016.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

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 20.1 is acceptable. No changes to the safety concerns, pharmacovigilance plan or risk minimisation measures have been made. The PRAC endorsed PRAC Rapporteur assessment report is attached.

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.

The CHMP endorsed the Risk Management Plan version 20.1 with the following content:

Safety concerns

Safety concerns	
Important Identified Risks	Infections with special reference to TB and

Safety concerns	
	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

Study / Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
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 and Other Anti-Rheumatic	To assess risk of infections, malignancies, and mortality in patients initiating abatacept vs. patients adding or switching to	Infections, infusion-related reactions, malignancies, autoimmune disorders, pregnancy, injection	Ongoing	Interim data submitted each Feb in summary report Final Study Report: Dec-2016

Study / Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
Therapies (IM101045B) *(non-interventional cohort, 3)*	biologics & DMARDs	reactions, combination biologic use, elderly		
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.	Infections, malignancies, mortality	Ongoing	Interim data submitted annually Final Study Report: Dec-2018

Study / Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
	non-biologic DMARDs			
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 cohort, 3)*	To assess abatacept patient demographics and incidence of malignancies, infections, infusion reactions, autoimmune events and mortality	Infections, infusion-related reactions, malignancies, autoimmune disorders, elderly	Ongoing	Interim data submitted each Feb in summary report Final Study Report: 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 Minimization Measures	Additional Risk Minimization Measures
Identified risks		

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
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 of the SmPC	Not applicable
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

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
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 and 5.1 of the SmPC (for powder for concentrate for solution for infusion) and sections 4.1, 4.8 and 5.1 of the SmPC (for solution for injection in pre-filled syringe and solution for injection in pre-filled pen).

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 applicant 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 sc. injection (EC Decision received on 4 October 2012).
- 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

Benefits

Beneficial effects

The pivotal study IM101226 demonstrated that s.c. treatment with abatacept + MTX provides a clinically significant benefit in MTX-naïve RA patients with highly active disease, in terms of sustained remission, in comparison with MTX monotherapy (remission rates, defined DAS28-CRP < 2.6, at month 12): 60.9 % vs 45.2 % for abatacept+ MTX compared to MTX alone, OR (95% CI) 2.01 (1.18 3.43), p<0.01). Results from the supportive study IM101023 with iv abatacept showed similar results (remission at 12 months in 41.4% vs 23.3% of patients in abatacept + MTX vs MTX groups, p<0.001).

Descriptive results on most of the secondary endpoints in both studies also favoured numerically the abatacept + MTX group.

In the main study the treatment with abatacept + MTX was associated with a smaller progression in structural damage, as reflected by mean post baseline MRI erosion score, and larger improvements in MRI osteitis and synovitis scores at Month 12 compared with the MTX monotherapy group (treatment differences = -1.22, 95% CI = [-2.20, -0.25], -1.43, 95% CI = [-2.68, -0.18], and 1.60, 95% CI = [-2.42, -0.78], respectively). In the supportive study evaluation of joint damage using the Genant modified Sharp score

(X-ray) demonstrated less progression in structural damage in the patients treated with abatacept + MTX than in the MTX-group: the mean change from baseline in radiographic total score and erosion score in abatacept + MTX group was 0.63 and 0.50 respectively and in MTX group 1.06 and 0.89 (p=0.040).

Further, a small, but significantly greater number of subjects achieved drug-free, DAS-defined remission at both 12 months of treatment and following 6 months withdrawal of RA treatment (co-primary endpoint) in the initial abatacept + MTX group compared to the MTX group. A total of 26% of subjects who were in remission at one year were able to maintain remission after 6 months of drug withdrawal and 12% of subjects maintained remission for 12 months after drug withdrawal.

Uncertainty in the knowledge about the beneficial effects

Although the analysis on the *second co-primary endpoint* (remission at 12 and at 18 months) showed similar results to those on the first co-primary endpoint in the pivotal study, an overall lower magnitude in efficacy rate was seen and results of the analysis were only of borderline significance. Thus, for the majority of patients complete withdrawal of all study medications led to relapse of remission, with the requested *post hoc* analyses showing that the risk of having a relapse after drug withdrawal was similar across the three study groups.

Overall, the results of the *secondary outcome variables* appeared to support those of the analysis on the co-primary endpoint with clinically relevant changes, but it should be noted that no formal statistical analyses were provided on any of these variables; only descriptive statistics was available.

Although at an average the study sample comprised patients with high RA disease activity as defined by the EULAR DAS28-CRP criterion of 5.2 and higher, the inclusion criteria targeted RA patients with a disease activity of > 3.2. High proportions of patients in both studies had the highest degree of severity, as defined by the EULAR criteria, (approximately 60 %, at an average 5.4 in the pivotal; over 80% in the supportive study). The remainder had moderate disease activity.

A subgroup analysis in study IM101226, based on levels of disease activity showed that the primary outcome, DAS28-CRP remission at Month 12 (proportion) was higher in the SC abatacept + MTX group compared to the MTX group, regardless of the level of disease activity at baseline. The estimated difference in response rates was similar in both subgroups of moderate and high disease activity, reflecting a similar benefit in the two populations. The *post hoc* analyses showed similar results for the supportive study IM101023.

Classification of RA according to the 2010 ACR/EULAR criteria was lacking and not an inclusion criterion in study IM101226. However, it was concluded that the inclusion criteria of the pivotal study correlated well with the ACR/EULAR criteria. This together with the diagnosis of early RA from the treating rheumatologist was considered strong enough evidence that the target population was appropriately diagnosed and classified with RA.

Risks

Unfavourable effects

Studies IM101226 and IM101223 provide 2 years of exposure to abatacept + MTX in each study, demonstrating the long-term safety of combination treatment in MTX-naïve patients. The AVERT study also provides safety data after drug withdrawal and re-exposure, with a low frequency of adverse events observed during the Withdrawal and Re-exposure Periods

Overall, the AE profiles of abatacept were similar between MTX naïve RA patients (the subject of this indication extension) and patients with RA in later lines of treatment (who responded inadequately to

previous therapy). The most common AEs in the main study in this application were nasopharyngitis, upper respiratory tract infections like sinusitis and urinary tract infections.

The incidence of anti-abatacept antibodies in the abatacept + MTX group was 2.9% in the Treatment Period, 37.7% in the Withdrawal Period, and 13.2% in the Re-exposure Period. The corresponding figures in the abatacept monotherapy group were slightly higher (5.0%, 44.1% and 13.3%). This is consistent with the assumed suppressive effect of MTX on ADA production. However, the overall immunogenicity was similar in both treatment groups (44.8% and 43.5%, respectively). The immunogenicity rate was thus particularly high in the Withdrawal Period (37.7% in the abatacept + MTX group and 44.1% in the abatacept monotherapy group).

Taken together, the safety data available from the randomized clinical trials and PM studies support a favourable safety profile of abatacept as a first line biologic. No new signals or clinically significant safety information have arisen study from study IM101226.

Uncertainty in the knowledge about the unfavourable effects

Average exposure for abatacept was 12.4 and 12.7 months for abatacept monotherapy and abatacept+MTX arms respectively in the Treatment Period in study IM101226. In the re-exposure period average exposure was 6.8 months for both abatacept arms.

Given that the mean exposure in the Treatment period was only just over a year, it is considered as a relatively short-term study. In the long term, infections and local injection site reactions are the key identified risks. Opportunistic infections, malignancies and autoimmune disorders remain the most important potential serious adverse effects for abatacept. Abatacept has an extensive risk management programme in place that links several registries, post marketing and clinical trial experience; these risk minimisation measures apply equally to the new proposed indication for abatacept and will reduce the uncertainties in the knowledge about the risks related to abatacept as a first line treatment in RA.

The rate of anti-abatacept antibodies was unexpectedly high in the pivotal study especially in the Withdrawal Period. Current knowledge dictates that immunogenicity status in abatacept treated patients does not have an effect on the efficacy and safety of abatacept. The analysis of clinical correlates provided limited information in this study due to the small number of ADA-positive patients during the treatment period, however the reported cases did not raise any concerns.

Effects Table

Table 29. Effects Table for abatacept in combination with methotrexate for the treatment of highly active and progressive disease in adults with rheumatoid arthritis not previously treated with methotrexate (data cut-off:27 October 2014)

Effect	Short Description	Unit	Abatacept + MTX	Abatacept	MTX	Uncertainties/ Strength of evidence	References
Favourable Effects							
Remission	DAS28-CRP < 2.6 at month 12	%	60.9	42.5	45.2	Following withdrawal of treatment at month 12 percentage of patients in remission at both months 12	IM101226

Effect	Short Description	Unit	Abatacept + MTX	Abatacept	MTX	Uncertainties/ Strength of evidence	References
						and 18 are of borderline significance	
Unfavourable Effects							
Infections and infestations	Nasopharyngitis	%	27.5	25.7	20.4	Small study, other risks known to be associated with abatacept such as serious infections (TB), infusion related and injection reactions also likely to apply	IM101226
	URI	%	14.1	9.6	8.6		
	Sinusitis	%	6.7	3.2	2.3		
Immunogenicity	Anti-abatacept antibodies	%					
	TP	%	2.9	5	--		
	WP	%	37.7	44.1	--		
	RP		13.2	13.3	--		

Abbreviations: MTX=methotrexate; DAS28=disease activity score of 28 joints; CRP=C-reactive protein; URI=urinary tract infection; TP=treatment period; WP=withdrawal period; RP= re-exposure period

Benefit-Risk Balance

Importance of favourable and unfavourable effects

A clinically meaningful sustained remission in a MTX-naïve RA population with an average high disease activity, has been demonstrated up to one year in patients treated with abatacept and methotrexate. Sub-population analysis revealed similar effects in patients with moderate disease activity at baseline (DAS-28 CRP between 3.2 and 5.1) and those with high baselined disease activity (DAS-28 CRP > 5.1) Remission is considered an optimal goal in RA and a valid and stringent endpoint. The efficacy rates and effect sizes were comparable to previously presented data on abatacept and other data on adalimumab and tocilizumab.

The safety profile of abatacept is already relatively well established. No new major safety concerns were identified in this population of MTX-naïve RA patients with highly active disease. Infections remain the primary identified risk associated with the use of abatacept also during the long term. Infusion-related reactions and injection reactions following iv and sc administration of abatacept respectively are also known identified risks. The risk management plan of abatacept, has adequate routine and additional risk minimisation activities to manage these risks. In addition, its pharmacovigilance plan consists of extensions of clinical trials, pharmacoepidemiological study based of several RA registers and standard post-marketing safety surveillance to further characterise potential risks such as malignancies, autoimmune diseases and progressive multifocal leukoencephalopathy.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

Abatacept in combination with MTX was more efficacious than MTX monotherapy across a wide range of clinical measures in study IM101226 including remission, improvement in physical function, and inhibition of structural progression. In addition, results from both IM101226 and IM101023 are consistent with the efficacy profiles of abatacept in MTX-IR and TNF-IR RA patients in other trials, as well as being consistent by direct and indirect comparisons to anti-TNF and anti-IL–6 agents evaluated in these populations. Indeed, to date, there have been no failed trials in the investigation of abatacept therapy in RA, with consistency in results across endpoints and across trials in various RA populations.

Safety results in studies of abatacept use suggest that the safety profile of abatacept therapy is comparable to that with other bDMARDs or anti-TNF agents.

Integrated analyses of the efficacy and safety data in MTX-naïve RA therefore indicate that the abatacept benefit/risk profile is favourable in patients with MTX-naive RA. The therapeutic benefit of abatacept is when used earlier in the disease process, was not associated with any observed additional risk. Earlier aggressive intervention with an effective therapy for the appropriate patient is also consistent with recent treatment guidelines in RA.

Based on the data available, abatacept in combination with methotrexate (MTX) is approvable for the treatment of highly active and progressive disease in adults with rheumatoid arthritis not previously treated with methotrexate.

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 for Orencia in combination with methotrexate (MTX) in the treatment of adults with rheumatoid arthritis (RA) who have highly active disease not previously treated with MTX. As a consequence, sections 4.1 and 5.1 of the SmPC (for powder for concentrate for solution for infusion) and sections 4.1, 4.8 and 5.1 of the SmPC (for solution for injection in pre-filled syringe and solution for injection in pre-filled pen) are updated based on results from AVERT study (IM101226). The Package Leaflet is updated accordingly. Moreover, the updated RMP version 20.1 has been agreed.

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