London, 21 May 2010
EMA/361627/2010

SCIENTIFIC DISCUSSION

FOR
Orencia

International non-proprietary name/Common name:
abatacept

Procedure No: EMEA/H/C/00701/II/0033

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

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1. Scientific discussion

1.1. Introduction

Abatacept is a fusion protein that consists of the extracellular domain of human 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 and thus inhibiting full T-cell activation.

In the EU, abatacept, in combination with methotrexate, is approved for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have had an insufficient response or intolerance to other disease-modifying anti-rheumatic drugs including at least one tumour necrosis factor (TNF) inhibitor. A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate.

The medicinal product is available as a 250 mg powder for concentrate for solution for infusion and is to be administered intravenously.

This type II variation was submitted to extend the adult patient population for which abatacept can be used to include MTX-naive patients with severe, active, and progressive early disease and MTX-inadequate responders (IR) in patients with moderate to severe active rheumatoid arthritis. The applicant did not request scientific advice in relation to this development. With regard to the paediatric development, the applicant has received a waiver for the condition "rheumatoid arthritis". As abatacept is a protein composed of natural amino acids, the product is exempt from the preparation of an Environmental Risk Assessment in accordance with the applicable guideline.

The initially applied for extension of indication read as follows:

"ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease modifying anti rheumatic drugs including methotrexate (MTX).

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

The finally approved extension of indication reads as follows:

"ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs including methotrexate (MTX) or a TNF-alpha inhibitor."

1.2. Clinical aspects

3.2.1 CLINICAL PHARMACOLOGY

The pharmacokinetics of abatacept in healthy adults and adults with RA are well characterized and are summarized in the current product information. Blood samples for further evaluation of the PK of abatacept were not collected in the relevant studies supporting this application.

For completeness, additional pharmacokinetic data was provided from several completed studies (IM101013, IM101128, IM101063, IM101015). None of this data were assessed to have impact on the product information.

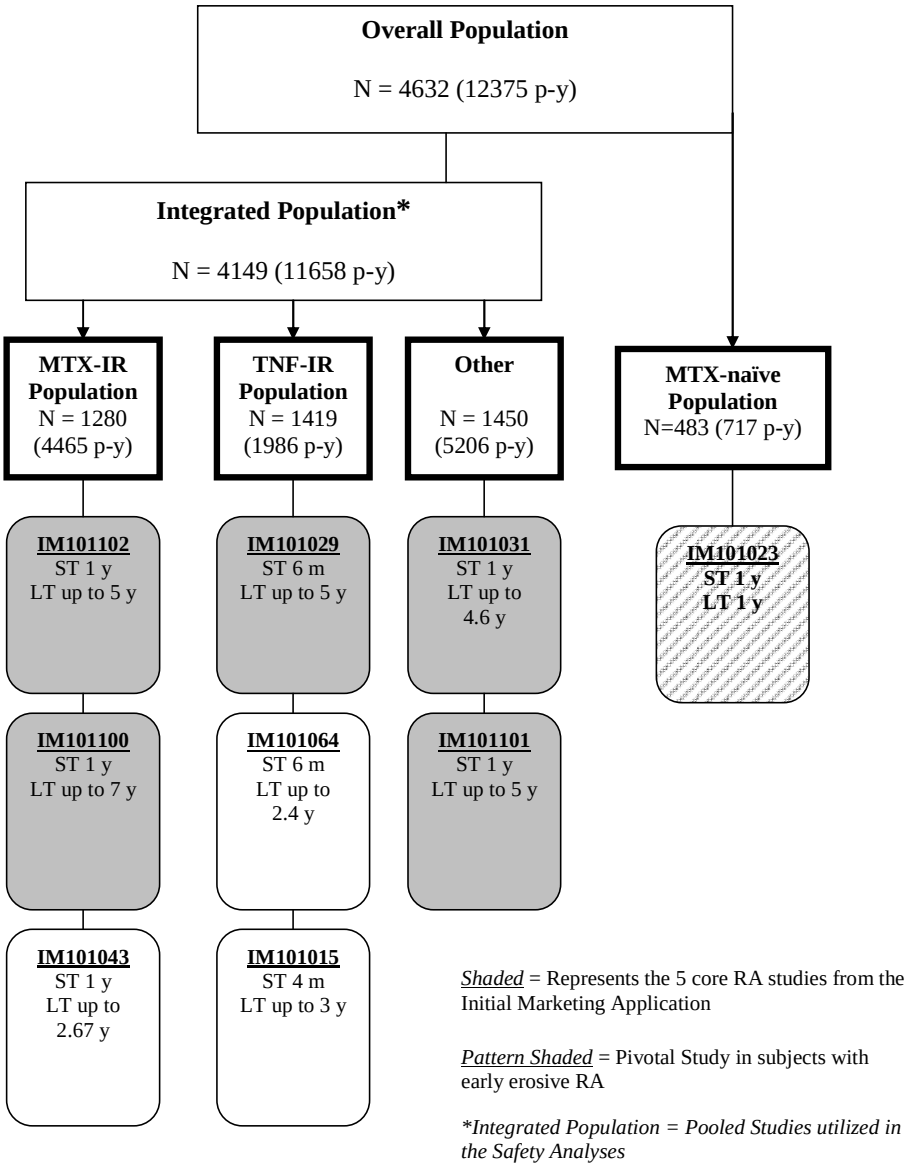
The pharmacodynamic effects of abatacept in adults with moderate to severe RA have been characterized and are summarized in the current product information. Pharmacodynamic data were also collected and assessed in IM101023.

3.2.2 CLINICAL EFFICACY

The initial marketing authorisation application (MAA) included data from placebo-controlled clinical studies investigating the use of abatacept for the treatment of rheumatoid arthritis after inadequate response to DMARDs including MTX (MTX-inadequate responders (IR) and TNF-antagonists (TNF-inadequate responders (IR)). These previously assessed data are also of relevance for the present extension application. The present application is additionally supported by the following studies:

- Efficacy and safety data from 4,632 subjects that have accumulated, through the long term (LT) periods of the pivotal Phase 2/3 studies in the MTX-IR and TNF-IR populations representing safety experience with 4,149 subjects for up to 8 years (11,658 person-years (p-y) of clinical study exposure); see Figure 1 for details about the studies covered.
- A new pivotal study (IM101023) conducted in 483 subjects with early RA (< 2 years of disease onset) with severe disease, prognostic factors predictive of progressive disease (erosion on x-ray and seropositive for RF or CCP, and who have not been previously treated with MTX (MTX-naive);
- Data from the post-marketing experience (~32,187 p-y experience), the majority of which was from regions where abatacept was approved for use without restriction of prior failure to other therapies.

Figure 1 Studies covered by the present variation application



Due to differences in the subject population across all studies, the efficacy data were not deemed appropriate for pooling. In addition, given that each of the studies was statistically powered, and that there was consistency of efficacy observed across all the studies (within each population), the additional value of pooling to interpret efficacy results would be limited.

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

Methotrexate-naive subjects

Main study

- **IM101023ST (1-year ST, short term) A Phase 3 Multi-centre, Randomized, Double-blind Study to Evaluate Remission and Joint Damage Progression in Methotrexate-naïve Early Erosive Rheumatoid Arthritis Subjects with Abatacept plus Methotrexate Compared with Methotrexate (1-year)**

METHODS

This was a multi-national, randomized, double-blind study to evaluate the efficacy and safety of abatacept in MTX-naïve subjects with early, erosive RA.

Study Participants

The subjects enrolled in this study must have been MTX-naïve prior to study start or their prior exposure to MTX must have been ≤ 10 mg per week for not more than 3 weeks and no dose for 3 months prior to signing the informed consent. The aim of the study was to recruit patients with severe progressive RA. The following inclusion criteria highlight the patient population:

- RA for ≤ 2 years
- high disease activity as defined by a tender joint count of at least 12, swollen joint count of at least 10, and a CRP of ≥ 0.45 mg/dL or ≥ 4.5 mg/L.
- seropositive RA (rheumatoid factor- or anti-CCP2 positive)
- erosive disease (evidence of erosion of the hands, wrists, or feet)

Treatments and randomisation

Subjects were randomized in a 1:1 ratio to receive abatacept (ABA, 10 mg/kg, weight-tiered dose based upon the subject's body weight from the screening visit immediately prior to the Day 1 visit) or placebo (PLA) for the first 12 months of treatment. In addition, both groups received methotrexat (MTX) and had their dose titrated to at least 15 mg per week not to exceed 20 mg per week. After the first 12 months of treatment, all subjects received the combination of ABA + MTX; however, the subjects, sites, and radiographic laboratory personnel remained blinded to the treatment received during the first 12 months of the study. The first 12 months of data from this study are presented in this document.

Subjects received study medication at every treatment period visit (Days 1, 15, 29, 57, 85, 113, 141, and every 28 days thereafter).

No adjustments in MTX or corticosteroids were permitted for the first 6 months of the study (unless the dose needed to be decreased due to toxicity). After 6 months of treatment, adjustments in corticosteroids (equivalent to a maximum dose of 10 mg/day prednisone) were permitted, as necessary. In addition 1 of the following DMARDs could have been added at the investigator's discretion: chloroquine, hydroxychloroquine, sulfasalazine, gold, or azathioprine. Analgesics were permitted, although no adjustments to study medication dose or schedule was permitted.

Objectives

The co-primary objectives for this study were to compare the clinical efficacy of abatacept used in combination with methotrexate (ABA + MTX) vs. placebo in combination with MTX (PLA + MTX) on the:

• Proportion of subjects who achieved remission at Month 12 of treatment, as defined by a DAS 28-CRP score < 2.6

• Joint damage progression measured by radiographic evaluation using the Genant-modified Sharp total score at Month 12 of treatment.

The secondary objectives included proportion of subjects with an ACR 50 response at Month 12, disease activity as measured by DAS 28-CRP score at Month 12, improvement in physical function

using the HAQ Disability Index defined by a reduction of at least 0.3 from baseline at Month 12, improvement in health-related quality of life using the Short Form 36 Questionnaire (SF-36) at Month 12, and inhibition of joint damage progression measured by radiographic evaluation using the Genant-modified Sharp erosion, and joint space narrowing (JSN) scores at Month 12.

Outcomes/endpoints

The DAS 28-CRP remission was evaluated at screening and at day 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365 (last visit of Year 1). Radiographs of the hands, wrists, and feet were performed at screening, Month 6, Month 12, and at the discontinuation visit. Other efficacy assessments (SF-36 and Fatigue VAS) were performed at screening, on days 1, 29, 85, 169, and 253. The Activity Limitation Questionnaire was completed at all study days in the first 12 months of the study except for Day 15.

Sample size

The group receiving ABA + MTX was compared with the group receiving PLA + MTX in subjects that were MTX-naïve at Month 12. Sample sizes were based on a 5% level (2-tailed) of significance. A total of 500 randomized subjects allocated in a 1:1 ratio to the active ABA + MTX group and the PLA + MTX group yielded a 99% power to detect a difference of 20% in DAS 28-CRP remission rate between the 2 groups at the 5% level. This power estimate assumed a response rate of 15% at Month 12 in the PLA + MTX group and an overall 15% drop-out rate. Based on the hierarchical testing procedure for the co-primary endpoints, this sample size allowed the detection of a treatment difference of 1.6 (common standard deviation of 5) with a power of 90% for the mean change from baseline in total score using the Genant-modified Sharp method.

Blinding (masking)

The first 12 months of this study was double-blinded. Primary analysis was performed at Month 12, but subjects, sites, and the central reading lab remained blinded to the treatment received during the first 12 months until the end of the study at Month 24.

Statistical methods

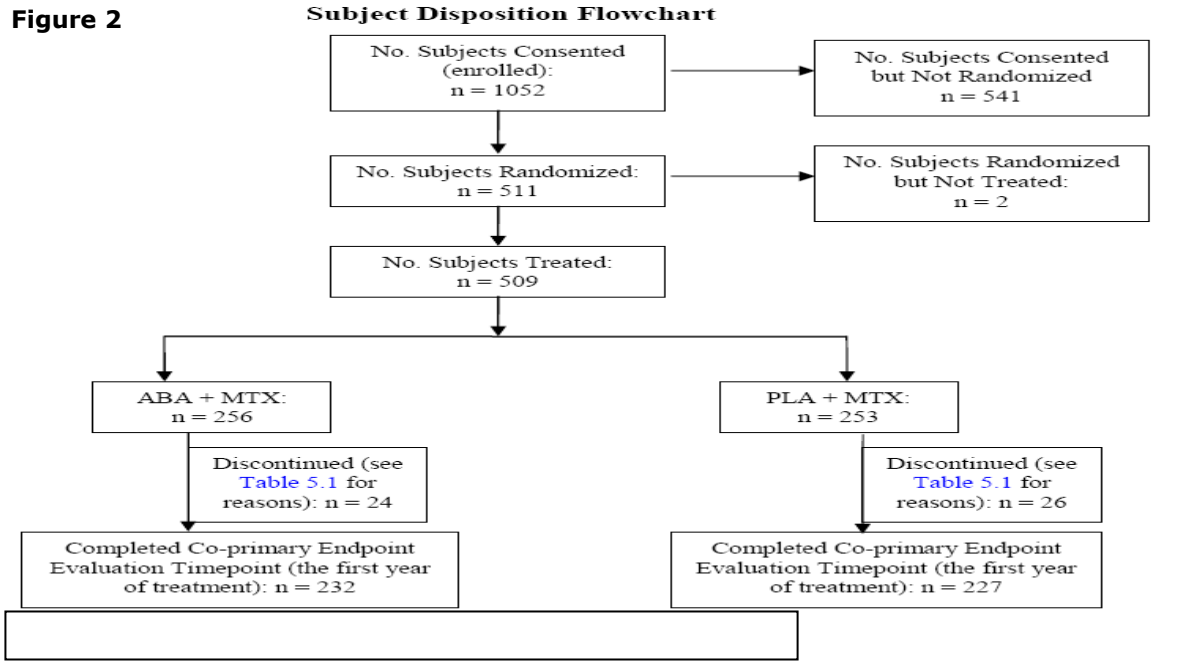
Measure of Interest at Year 1	**Analysis Method**
Remission rate (DAS 28-CRP < 2.6), ACR 50 response, MCR rate, and HAQ response rate	Continuity corrected Chi-square test, p-value, 95% CI for treatment difference
Radiographic total, erosion, and JSN scores	Rank-based ANCOVA, p-value, mean, SD, median, upper and lower quartiles
DAS 28-CRP and SF-36 (PCS and MCS)	ANCOVA, adjusted mean, SE, 95% CI for treatment difference, p-value

Co-primary efficacy analysis include, in the order of sequential testing, comparison between abatacept in combination with methotrexate and a placebo control of methotrexate alone in remission rate (EULAR-defined DAS28 remission) at twelve months (Day 365) and total sharp scores using the Genant-modified Sharp method at twelve months (Day 365). A sequential testing procedure was employed for testing the co-primary hypotheses according to the hierarchy specified above. For each of the tests, the nominal type I error rate is set at 5%, therefore this sequential testing procedure preserves the overall type I error rate at 5%.

RESULTS

Participant flow

Figure 2



The discontinuation rates (Table 2 [referred to in the diagram as table 5.1]) were similar across treatment groups: 9.4% (abatacept) and 10.3% (placebo). This data rule causes no meaningful bias in favour of abatacept over placebo.

Table 2 **Subject Disposition: Reasons for Discontinuation During the First Year of Treatment: All Randomized and Treated Subjects**

	Number (%) of Subjects		
	Abatacept N=256	Placebo N=253	Total N=509
Number Discontinued	24 (9.4)	26 (10.3)	50 (9.8)
Death	2 (0.8)	2 (0.8)	4 (0.8)
Adverse Event	9 (3.5)	11 (4.3)	20 (3.9)
Lack of Efficacy	0	8 (3.2)	8 (1.6)
Lost to Follow-up	2 (0.8)	1 (0.4)	3 (0.6)
Withdrawal of Consent	7 (2.7)	3 (1.2)	10 (2.0)
Subject no longer meets study criteria	1 (0.4)	0	1 (0.2)
Poor/Non-compliance	0	0	0
Pregnancy	2 (0.8)	0	2 (0.4)
Administrative reason by sponsor	0	0	0
Other	1 (0.4)	1 (0.4)	2 (0.4)
Number Completed First Year of Treatment	232 (90.6)	227 (89.7)	459 (90.2)

The patient follow up rates, for both study groups, are over 90% at 12 months, the time of the primary efficacy analysis.

Conduct of the Study and Numbers analysed

The original protocol (06-May-2005) was amended eight times.

During the first 12 months of treatment, 44 subjects (20 subjects on ABA + MTX and 24 subjects on PLA + MTX) had significant protocol deviations. Since fewer than 10% of subjects in either treatment group had a significant protocol deviation, a 'per-protocol' population was not generated.

A scoring technique based on the Genant-modified Sharp algorithm was used to assess the radiographic data. 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).

Baseline data

The baseline demographic and disease and other characteristics were similar for both treatment groups. The majority of subjects were white females, approximately 50 years old (table 3).

Table 3 Baseline Demographic Characteristics: All Randomized and Treated Subjects

		Abatacept N = 256	Placebo N = 253	Total N = 509
Age (years)	Mean	50.1	49.7	49.9
Gender	Male Female	60 (23.4%) 196 (76.6%)	54 (21.3%) 199 (78.7%)	114 (22.4%) 395 (77.6%)
Duration of RA	Mean (SD)months	6.2 (7.5)	6.7 (7.1)	6.5 (7.3)
Race Caucasian	(%)	202 (78.9)	219 (86.6)	421 (82.7)
Tender Joints	Mean (SD)	31.3 (14.8)	30.8 (14.0)	31.0 (14.4)
Swollen joints	Mean (SD)	22.9 (11.3)	21.9 (10.1)	22.4 (10.8)

With regard to previous and baseline treatments, in general the proportions of subjects who used anti-rheumatic medications at screening/enrollment and at randomization (Day 1) were generally comparable in both treatment groups. Most subjects in both groups were exposed to prior corticosteroids and NSAIDs. The number of subjects who received MTX prior to screening was ABA + MTX: 8 subjects; PLA + MTX: 2 subjects.

Regarding concomitant therapy, in general, the proportion of subjects who received corticosteroids (oral and/or injectable) and NSAIDs during the first 12 months of treatment were comparable for both groups. The proportion of subjects who received other DMARDs was higher in the PLA + MTX group at Days 1 to 169 (5.1%) and Days 170 to 365 (8.7%) compared with the ABA + MTX group (2.7% and 3.5%, respectively).

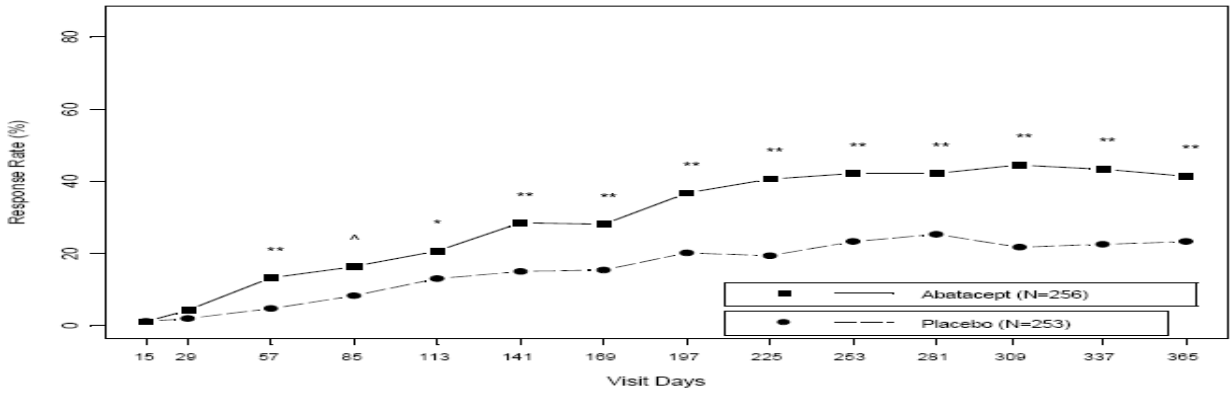
Outcomes and estimation

When compared with the PLA + MTX group, the ABA + MTX group met both of the pre-specified clinical efficacy co-primary endpoints; the results are summarized below:

Remission (DAS 28-CRP) at Month 12

Analysis of the primary efficacy variable for this study demonstrated that the percent of subjects achieving remission, as defined by DAS 28-CRP < 2.6, at Month 12 was significantly higher in the ABA + MTX group compared with the PLA + MTX group: 41.4% vs. 23.3%, $p < 0.001$). The statistical significance in the remission rate between the 2 groups was noted as early as Day 57 and continued through Day 365 (Figure 2).

Figure 3 **DAS 28-CRP Remission Over Time: All Randomized and Treated Subjects**



Genant-modified Sharp Total Score at Month 12

Subjects in the ABA + MTX group had significantly less progression of structural damage compared with the PLA + MTX group as demonstrated by the mean change from baseline in total score at Month 12 ($p = 0.040$). The mean change from baseline in total scores at Month 12 for the ABA + MTX group (0.63) was almost half of that in the PLA + MTX group (1.06) suggesting an approximate 50% reduction on the evolution of radiographic change when subjects were treated with ABA + MTX.

The mean change in Total Sharp score (TSS) at 12 months was significantly lower in patients treated with abatacept plus methotrexate compared to those treated with methotrexate plus placebo. At 12 months 61% (148/242) of the patients treated with abatacept plus methotrexate and 53% (128/242) of the patients treated with methotrexate plus placebo had no progression (TSS ≤ 0).

With reference to other secondary endpoints, the following data was obtained:

ACR Response

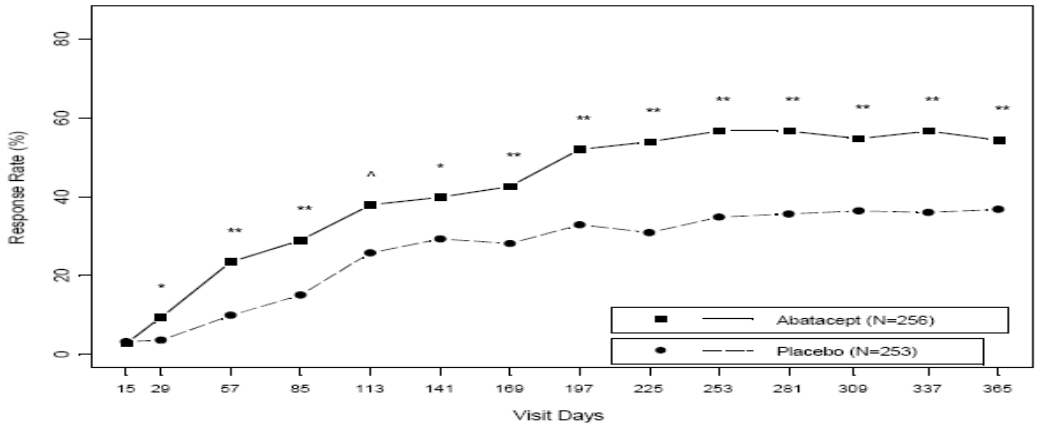
At Month 12, an ACR 50 response was achieved by significantly more subjects in the ABA + MTX group compared with the PLA + MTX group: 57.4% (CI 51%, 63%) versus 42.3% (CI 32%, 48%), $p < 0.001$.

A significantly greater proportion of subjects treated with ABA + MTX had greater improvements in ACR 20, ACR 50, ACR 70, and ACR 90 than subjects treated with PLA + MTX at Days 169 and 365. Continued improvement in ACR responder rates was observed between Months 6 and 12.

Low Disease Activity (LDA)

Statistical significance in the LDA rate between the 2 groups was noted as early as Day 29 and continued through Day 365 (Figure 4).

Figure 4 **Low Disease Activity Over Time: All Randomized and Treated Subjects**



** - significant at the 0.001 level, ^ - significant at the 0.01 level; * - significant at the 0.05 level Program Source:

Similar to the DAS 28-CRP remission rate and LDA results, a greater proportion of subjects in the ABA + MTX group were in remission or with LDA compared to the subjects in PLA + MTX group during the first 12 months of treatment based on DAS 28-ESR.

Physical Function (HAQ)

At Month 12, significantly more subjects in the ABA + MTX group compared with the PLA + MTX group (71.9% vs. 62.1%, p = 0.024), achieved a HAQ response that was clinically meaningful. Statistically significant responses were observed as early as Day 29 for the ABA + MTX group and continued through Month 12. Greater mean reductions from baseline were observed for the HAQ disability index and its subscales at all timepoints for the ABA + MTX group compared with the PLA + MTX group.

Secondary and Tertiary Radiographic Evaluation Variables

Subjects in the ABA + MTX group had significantly less progression of structural damage compared with the PLA + MTX group as demonstrated by the mean change from baseline erosion score at Month 12 (0.50 vs. 0.89; p = 0.033). There was less progression of structural damage as demonstrated by the mean change from baseline in the JSN score in the ABA + MTX group (0.13) as compared with the PLA + MTX group (0.17) at Month 12; however, the difference was not statistically significant. At Month 6, subjects in the ABA + MTX group had less progression of structural damage compared with the PLA + MTX group as demonstrated by the mean change from baseline erosion (ABA + MTX = 0.40; PLA + MTX = 0.62), JSN (ABA + MTX = 0.08; PLA + MTX = 0.12), and total (ABA + MTX = 0.47; PLA + MTX = 0.74) scores. A greater proportion of subjects in the ABA + MTX group (155 of 242 subjects; 64.0%) were without radiographic progression (≤ 0 changes from baseline erosion scores) at Month 12 as compared with subjects in the PLA + MTX group (133 of 242 subjects; 55.0%).

Health-related Outcomes

In the Short Form 36 Questionnaire (SF-36) For subjects treated with ABA + MTX compared with those treated with PLA + MTX, significantly greater improvements from baseline were observed in the PCS (p = 0.005) and MCS (p = 0.046) summary measures at Month 12. Greater improvements in physical and mental subscales were observed at Month 12 for the ABA + MTX group compared with the PLA + MTX group.

MTX-inadequate-responders (MTX-IR population)

In the MTX-IR population, clinically and statistically significant efficacy of abatacept over placebo in the MTX-IR population was demonstrated during the ST (double-blind) period of all core RA as well as supportive RA studies. The studies were already assessed by the CHMP in the context of the initial; marketing authorisation application; for further details see this assessment report. In addition, the following analyses were performed for the present application:

Comparative ST Response Rates in MTX-IR

A Bayesian meta-analysis was performed to estimate the efficacy of abatacept relative to other biologic DMARDs (etanercept, infliximab, adalimumab, and rituximab) in the management of patients with RA and an inadequate response and/or intolerance to non-biologic DMARDs. A systematic literature search was performed in order to identify randomized controlled studies of abatacept and other biological DMARDs in the treatment of rheumatoid arthritis. Data were extracted from all qualifying studies (13 in total) with the following features: placebo-controlled studies of at least 24-week duration in adult RA patients who have had prior insufficient response and/or intolerance to non-biologic DMARDs.

The data seem to indicate that abatacept has similar efficacy when compared to infliximab, etanercept, and rituximab. There is a suggestion that abatacept may be less efficacious than adalimumab, however this was not rigorously established. In addition, this higher efficacy observed in adalimumab may be driven by 1 small Phase 2 study (n=129) in which adalimumab reported an exceptionally high ACR50 response relative to its larger Phase 3 studies.

Comparative LT Response Rates in MTX-IR

A literature search on the LT efficacy results from open-label extension studies of TNF-antagonists was conducted to broadly assess the LT efficacy of abatacept as compared to the currently approved biologics for treatment of RA patients with inadequate response to at least 1 DMARD. Based on this comparison, it appears that the retention rate at the end of 4 years of LT therapy were comparable or higher in the abatacept study (73%) compared to the 3 TNF-antagonists (56% to 74%). In addition, the ACR50 and DAS28 response rates were comparable or higher in the abatacept study compared with the 3 TNF-antagonists.

The MAH concluded that indirect comparison of the efficacy of abatacept to the 3 TNF-antagonists indicates that the relative benefits of abatacept are comparable to TNF-antagonists in the MTX-naive population, differences in subject disease characteristics notwithstanding and in the MTX-IR population during ST use. After 4 years of LT therapy, in the MTX-IR population, abatacept demonstrated more favourable maintenance of LT efficacy, as evident both the higher magnitude of the absolute response and retention rates.

TNF-antagonist-inadequate-responders (TNF-IR population)

Supportive study

- **Long term IM101064LT A Phase 3, multi-centre, open-label study to evaluate the efficacy, tolerability, and safety of abatacept in subjects with active rheumatoid arthritis on background non-biologic DMARDs who have an inadequate response to anti-TNF therapy and have limited therapeutic options**

This study can be considered only supportive for the assessment of efficacy of abatacept because of the methodological limitation (uncontrolled, no formal statistical analysis performed, low retention rate of subjects etc).

Patients included had active RA and had an inadequate response to previous (washout for at least 2 months; n=449) or current (no washout period; n=597) TNF-antagonist therapy (Study VII). The primary objective of the long-term extension period is to assess the long-term safety and tolerability of abatacept in subjects who have completed the initial 6-month open-label treatment period. The results demonstrated that the incidence of AEs, SAEs, and discontinuations due to AEs during 6 months of treatment, was similar between those who were previous and current TNF-antagonist users at enrollment, as was the frequency of serious infections.

Discussion on clinical efficacy

Abatacept has been investigated in clinical trials for the treatment of moderate to several active rheumatoid arthritis in adult patients after inadequate response to DMARDs including MTX (MTX-inadequate responders (IR) and TNF-antagonists (TNF-inadequate responders (IR)). These data have been assessed in the context of previous submissions and are also of relevance for the present extension application.

Additionally, with the present application the applicant provided efficacy data from a single controlled clinical trial (IM101023). The aim was to assess the efficacy and safety of abatacept in combination with methotrexate (ABA + MTX) compared with placebo and MTX (PLA + MTX) over the first 12 months of a 24-month study in MTX-naïve subjects with early, erosive rheumatoid arthritis (RA), seropositivity for RA, and poor prognostic factors for disease progression in support of the proposed indication. With regard to this study, the CHMP made the following observations:

A concern related to the choice of the control treatment was raised by the CHMP, namely whether it was optimal to choose MTX monotherapy over combination treatment (MTX + sulfasalazine + others) as the control population may be undertreated. The results of available comparative trials provided by the MAH support the use of a combination of DMARDs as the comparator. However, given the precedent of other studies using biologic compounds in early RA, the various design and interpretability issues of the different DMARD studies, and concerns around the global acceptability of a combination regimen, it was considered acceptable to have MTX monotherapy as the comparator arm, since it is widely accepted as the standard of care for the treatment of RA, and its optimal use is well defined with regard to dosage. The differences, furthermore, between abatacept (abatacept + MTX) and active control (MTX + placebo) were robust, making it unlikely that an active control using combined therapy would have resulted in no difference. However, using this type of control in IM101023 was considered to argue against the use of abatacept as first-line (mono) therapy.

The baseline demographic, clinical and other characteristics appear to be well balanced between the study groups implying successful randomisation. The study design, inclusion criteria, selected end points and the undertaken analysis are in general considered relevant for the intended aim of the study, and comply with guidance and are comparable to pivotal studies for other biologic therapy approved for the first line indication and appear even more stringent for abatacept on the criteria intended to identify a population with early progressive disease (with the exception that disease duration in the etanercept study, which was much longer than all other studies). In addition, the abatacept study involved a patient population with severe disease. Only 11.4% of subjects had DAS28 of ≤ 5.1 at study entry. The majority of subjects (88.4%) entered the study with severe disease, with DAS28 >5.1. The mean (SD) DAS28 (CRP) was 6.3 (1.0) for the entire study population. However, the baseline radiographic scores of this study were not compared to similar studies with other biologicals due to differences in radiographic scoring systems used across the studies.

The CHMP noted that the term "early erosive rheumatoid arthritis" is poorly defined in literature and that no official consensus of the criteria exits. To define an "early" population and to determine the inclusion criteria, the MAH has referred to other approved biological drugs with studies in the "early"

population. In a comparison of the inclusion criteria for studies in comparable RA populations across different biologic therapies the MAH showed that the study IM101023, has similar and even the most stringent inclusion criteria for "early erosive rheumatoid arthritis" for the duration of RA, and requirements for factors predictive of severe progressive disease such as positive RF or positive anti-CCP, CRP and erosion on x-ray at baseline.

As it was considered relevant to the design of the indication/target population, exploratory post hoc subgroup analyses based on the severity of the disease (signs and symptoms of RA, degree of functional impairment and the rate radiological damage) were requested in an attempt to see whether the resulting effect of the combination treatment was more of a result of a certain subgroup of patients and further, whether a subgroup of patients could benefit from the treatment more than others. The MAH was able to show that the results were not driven by any one subgroup of patients. The fact, that the therapeutic effect was seen in all categories of disease severity, supported the robustness of the results of the study sample and the homogeneity of the study population.

In this phase three clinical trial the MAH has chosen to use the DAS28–CRP as the first co primary efficacy endpoint. This outcome measure is validated, clinically relevant and can be considered more stringent than ACR50 (50% decrease in treatment activity), which has previously been used as the primary efficacy endpoint in abatacept treatments trials by the MAH.

DAS28-CRP remission showed significant effect at twelve month, the time of the primary efficacy analysis, with the percent of subjects achieving remission, as defined by DAS 28-CRP < 2.6, being significantly higher in the ABA + MTX group compared with the PLA + MTX group: 41.4% vs. 23.3%, $p < 0.001$. The statistical significance in the remission rate between the 2 groups was noted as early as Day 57 and continued through Day 365. Initiation of abatacept with MTX in MTX naive patients with early and severe RA with prognostic factors predictive of progressive disease resulted in clinically meaningful and statistically significant benefits compared to initiating MTX alone as assessed by the different measures of RA disease activity (DAS28CRP, ACR, HQ, SF-36)

The second structural co primary end point showed consistent results with the first primary outcome, although 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 using the Genant modified Sharp score is well documented in many clinical studies as a robust tool. Less progress in structural damage was found in the patients treated with abatacept in combination with MTX than in the group initially treated with placebo + MTX. The mean change from baseline in radiographic total score and erosion score in ABA+MTH group was 0.63 and 0.50 respectively and in the PLA+MTX group 1.06 and 0.89. The prevention of erosions in early rheumatoid arthritis is more important than the effect on joint narrowing. Less progression was seen also in the follow up period. The progression rate in both groups was rather slow, which is a desired result. The importance of the result is that early treatment with abatacept gives additional benefit in protecting joint damage than methotrexate alone. This is shown in the higher percentage of non-progressors (92.8% for erosion score) in those patients who were non-progressors both after the initial double-blind period and after the open-label period in comparison with those patients initially treated with only MTX (87.0%). In these patients with early active disease even rather small differences are clinically meaningful. Although, abatacept + MTX was marginally superior to MTX alone in reducing joint damage as judged by x-rays, reservations on the magnitude of the effect, still remains.

The across study comparisons of the radiographic co primary endpoints are, however, difficult to conduct because of differences in the methodology and the inherent inter-study-variability in x-ray evaluation. For these reasons, the MAH has not made an attempt to compare the individual studies. Thus, the size of the abatacept treatment effect as compared to other therapies cannot be fully

estimated on the basis of this submission. Long term data beyond 2 years are outstanding. Unfortunately the one comparative trial (IM101-043), the MAH refers to (see safety section), doesn't contain the progression rate of erosion among the efficacy parameters. However, according to the results of the 5-year follow-up of IM101102 trial (see safety section), radiographic progression remained stable over the observation period. On this background, however, the first line indication appears premature.

Controlled long term data beyond the duration of 12 months of this double blind period of this pivotal study is lacking, but in the open label follow up studies the effect of abatacept appears to be maintained especially on the primary efficacy outcome measure of DAS28CRP (IM101064LT and IM101023LT).

In the absence of direct comparative data, the MAH has compared the study design and results of IM101023 to pivotal trials of other biological therapies. Furthermore, the MAH refers to two new independent comparative meta-analyses from the literature, including new data from the Keystone et al (abstract), and the Cochrane reviews. The comparison of the study design and inclusion criteria of the study IM101023 to the corresponding pivotal studies of TNF alpha inhibitors shows that the studies are alike in their key features and results. The study IM101023 results support the conclusions of the meta-analysis and the Cochrane reviews, which conclude that abatacept is similar with respect to clinical efficacy compared to other tested biologic agents (with the exception of anakinra that is generally regarded as less effective). While meta-analyses have their limitations, they are extensively used in the evidence-based medicine. In such a meta-analysis *(Singh et al, 2009)*, 31 studies (abatacept n = 7 studies; adalimumab n = 8 studies; anakinra n = 5 studies; etanercept n = 4 studies; infliximab n = 4 studies; rituximab n = 3 studies) were compared. According to this analysis, the mean efficacy (in terms of OR - reaching remission, i.e. ACR50) was similar to infliximab and lower than adalimumab or rituximab; the safety was similar or better than that of the others. Based on 95% CI, these differences, however, are not significant.

3.2.3 Clinical safety

The nine clinical studies contributing to the safety assessment are outlined below (see Figure 5):

1) Open-label, LT period data from 5 core RA studies (IM101102, IM101100, IM101029, IM101031, and IM101101)

The data from the double-blind, controlled, ST period of these studies were previously submitted as part of the initial dossier leading to abatacept's approval in adult RA. The key focus in this document is based on the LT data. The abatacept safety experience for up to 8 years across these studies allow for LT safety assessment over time. Subjects who were inadequate responder to a prior DMARD therapy (including MTX and/or TNF-antagonist) were enrolled in these studies.

2) LT data from 3 supportive studies (IM101043, IM101064, and IM101015)

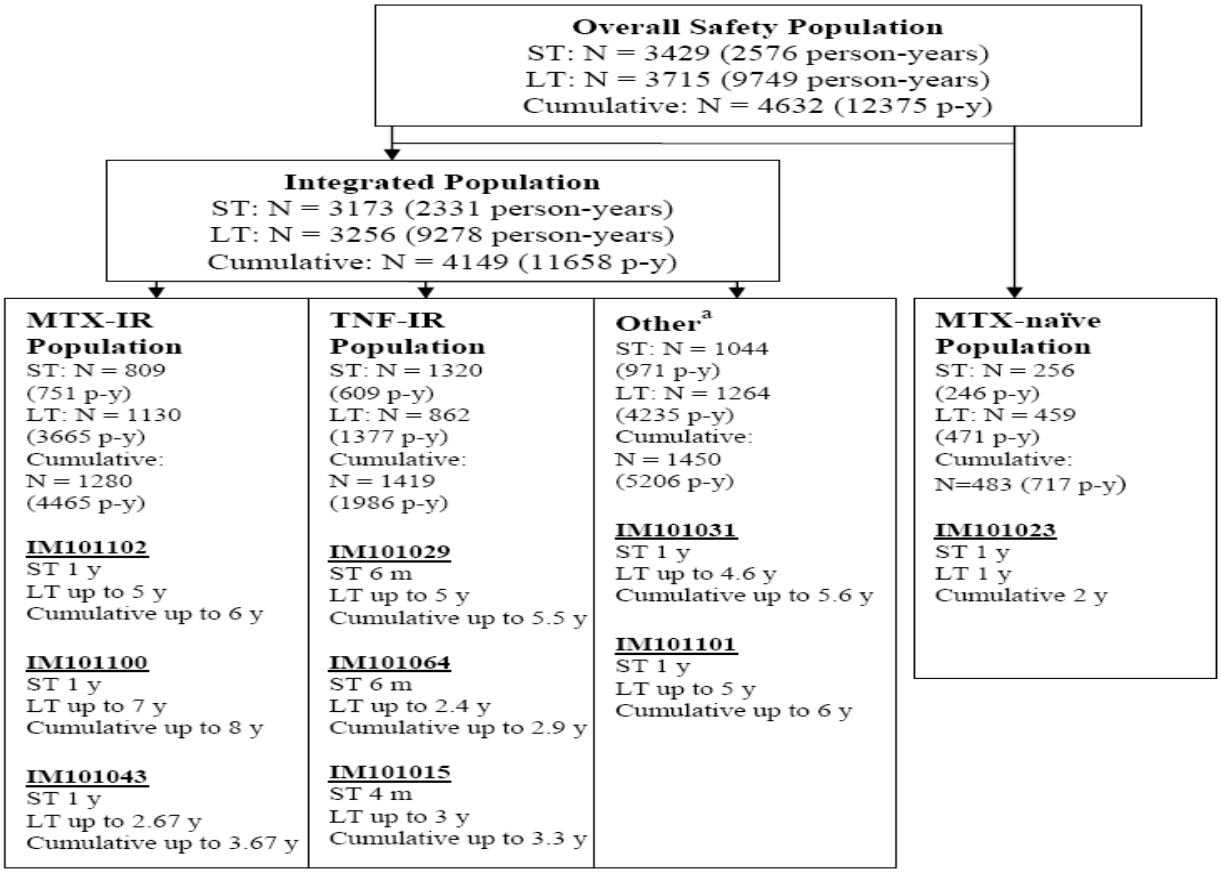
These studies were ongoing at the time of the initial submission and, thus, were not part of the clinical development program that supported the initial approval of abatacept for the treatment of RA. The data from the ST periods of these studies has subsequently been submitted. The key focus in this document is based on the LT abatacept safety experience (up to 3.67 years) from these studies. Subjects who were inadequate responder to a prior MTX and/or TNF-antagonist therapy were enrolled in these studies.

3) ST and LT data from IM101023

This study assessed the safety of abatacept in combination with MTX vs. MTX monotherapy in subjects with early RA (<2 years). The subjects were MTX-naïve with erosions and seropositivity (anti-CCP2

and/or RF). The safety data from this study have not previously been submitted. The data presented by the MAH includes results from both the ST and LT periods. Post-marketing data are based on abatacept experience in RA and juvenile idiopathic arthritis (JIA) patients.

Figure 5 **Safety Data Source - Abatacept-treated Subjects**



Safety results of IM101023ST

- Overall AEs**:** The overall proportion of AEs was similar for both groups (ABA + MTX: 84.8%; PLA + MTX: 83.4%).

- Serious adverse events and deaths

Deaths

Deaths were reported in 2 subjects (0.8%) in the ABA + MTX group and 4 subjects (1.6%) in the PLA + MTX group in the first 12 months of the study. In subjects receiving ABA + MTX the investigator reported the relationship to the investigational drug as probable. Two (2) of the 4 deaths in the PLA + MTX group were reported to have discontinued due to an AE rather than due to death.

Other Serious Adverse Events

A similar proportion of SAEs was observed for the ABA + MTX group (7.8%) compared with the PLA + MTX group (7.9%). A small number of subjects in each group had SAEs considered related to study medication (ABA + MTX: 2.0%; PLA + MTX: 2.4%) or were discontinued from the study due to a SAE (1.2% of subjects each in the ABA + MTX and PLA + MTX groups). In the ABA + MTX group, no single SAE was reported for > 2 subjects, the most frequently reported SAEs were in the infections and infestations SOC (2.0% incidence in both groups).

Infections and infestations were reported as SAEs in the same number of subjects in the ABA + MTX and PLA + MTX groups (5 subjects in each group). There were more subjects with pneumonia in the PLA + MTX group (1.2%) compared with the ABA + MTX group (0.4%). Gastroenteritis occurred as a single case and was equally distributed in both groups. Cellulitis, lung infection pseudomonal, and postoperative wound infection were single cases in the ABA + MTX group while breast cellulitis and staphylococcal infection were single cases in the PLA + MTX group. A malignant neoplasm (pancreatic carcinoma) was reported as an SAE in 1 (0.4%) subject in the ABA + MTX group compared with none in the PLA + MTX group. This event was considered not likely related to study medication and study medication was discontinued due to this event, which did not resolve. Neoplasms (benign and unspecified) were reported as SAEs in 2 (0.8%) subjects treated with ABA + MTX and none in the PLA + MTX group.

- Adverse Events Leading to Discontinuation of Study Therapy

A similar proportion of subjects in the ABA + MTX group (91%) compared with the PLA + MTX group (90%) completed the first 12 months of the study. A similar number of subjects discontinued due to AEs (ABA + MTX: 8 [3.1%] subjects, PLA + MTX: 11 [4.3%] subjects). The categories of AEs that most often led to discontinuation were: respiratory, thoracic and mediastinal disorders and skin and subcutaneous tissue disorders (2 [0.8%] subjects, each) in the ABA + MTX group. Respiratory, thoracic and mediastinal disorders (5 [2.0%] subjects) and gastrointestinal disorders (2 [0.8%] subjects) were the most common AEs leading to discontinuation in the PLA + MTX group.

- Adverse Events of Interest

Infections

There was a similar incidence of all serious infections/infestations in the ABA + MTX and PLA + MTX groups (5 subjects, 2.0% in each group). Infections/infestations were reported by 51.6% of subjects treated with ABA + MTX compared with 54.9% of subjects treated with PLA + MTX. The most common infections in both groups were upper respiratory tract infection (ABA + MTX: 10.2%; PLA + MTX: 10.3%) and nasopharyngitis (ABA + MTX: 8.2%; PLA + MTX: 10.3%). Almost all of the infections were mild (ABA + MTX group: 29.7%; PLA + MTX group: 26.5%) or moderate (ABA + MTX group: 20.3%; PLA + MTX group: 26.1%). Severe infections were reported by 4 (1.6%) subjects in the ABA + MTX group and 5 (2.0%) subjects in the PLA + MTX group. Very severe infections were reported by no subjects in the ABA + MTX group and 1 (0.4%) in the PLA + MTX group. There were no opportunistic infections, like TB or fungal infections, protozoal infections, or atypical presentations of infections reported in any subject receiving abatacept. However, there was a single case of pseudomonas pneumonia with ABA + MTX treatment in this study. There were no subjects in the ABA + MTX group that discontinued due to infections/infestations during the first 12 months of the study compared with 1 (0.4%) subject (preferred term: pneumonia) in the PLA + MTX group.

Neoplasms: Benign, Malignant, and Unspecified

There was 1 (0.4%) malignant neoplasm (pancreatic carcinoma) reported in the first 12 months of treatment with ABA + MTX and none reported for PLA + MTX. In addition, benign and unspecified neoplasms were reported in 10 subjects: 6 (2.3%) subjects in the ABA + MTX group and 4 (1.6%) subjects in the PLA + MTX group in the first 12 months of treatment. Skin papilloma was most frequently reported in the ABA + MTX group (2 subjects) with no occurrences in the PLA + MTX group.

Autoimmune Disorders (Pre-specified)

Autoimmune related disorders (pre-specified) were reported with similar frequency (ABA + MTX: 2.3%; and PLA + MTX: 2.0%). The most frequent were musculoskeletal and connective tissue

disorders (preferred terms: Sjorgen's Syndrome and systemic lupus erythematosus [SLE]) occurring in both groups (1 event [0.4%], in each group). The 2 events of Sjorgen's Syndrome were considered to be mild intensity and unrelated to study medication; subjects were treated and no further action was taken.

Infusional Adverse Events (Pre-specified)

Acute Infusional AEs: The overall frequency of acute infusional AEs (pre-specified) was higher in the ABA + MTX group (6.3%) compared with the PLA + MTX group (2.0%). Nervous system disorders were reported in 6 (2.3%) subjects in the ABA + MTX group compared with 3 (1.2%) subjects in the PLA + MTX group. Specifically, dizziness was reported in a greater proportion of subjects in the ABA + MTX group (2.0%) compared with the PLA + MTX group (0.8%). Headache was reported with similar frequency (0.4%, in each group) in both treatment groups. General disorders and administration site conditions were reported in 5 (2.0%) subjects in the ABA + MTX group and none of the PLA + MTX group. The majority of acute infusional AEs (pre-specified) were of mild to moderate severity. A total of 1 (0.4%) subject in the ABA + MTX group compared with none in the PLA + MTX group experienced acute infusional AEs (pre-specified) considered by the investigators to be severe ([preferred terms] urticaria).

Peri-infusional AEs: The overall frequency of pre-specified peri-infusional AEs was higher in the ABA + MTX group (12.5%) compared with the PLA + MTX group (9.9%). The majority of peri-infusional AEs (pre-specified) were of mild to moderate severity. A total of 2 (0.8%) subjects in the ABA + MTX group compared with none in the PLA + MTX group experienced severe peri-infusional AEs (pre-specified) ([preferred terms] urticaria and headache, respectively).

- Laboratory findings

Blood and urine samples for haematology, serum chemistries, and urinalysis were collected during the study. In addition, pregnancy tests were performed. No safety issues concerning laboratory testing were identified.

- Immunological events

Blood samples for immunogenicity assessments were obtained just prior to the start of the IV infusion of study medication at the following times during the first 12 months of the study: baseline (Day 1), Month 6, Month 12, and again 28, 56, and 85 days after the last infusion for subjects who withdrew from the study prematurely during the study drug treatment period.

Serum samples (n = 795 and n = 798) from ABA + MTX-treated, MTX-naïve, early, erosive RA subjects were analyzed by ELISA to detect antibodies against the whole molecule (i.e., both the CTLA4 and Ig portion [anti-abatacept antibody]) or solely to the CTLA4 portion (anti-CTLA4-T antibody). A total of 4 of 249 subjects (1.6%) demonstrated anti-abatacept antibodies; 3 of the 4 subjects were positive for the anti-abatacept antibody response (IgG specificity) and 1 of the 4 subjects was positive only for the anti-CTLA4-T antibody response (CTLA4-specificity). Of the 3 subjects with anti-abatacept antibodies, 2 subjects demonstrated anti-abatacept antibodies at both Month 6 and 12; 1 subject demonstrated anti-abatacept antibodies only at Month 12. Seropositivity for the subject with anti-CTLA4-T antibodies was demonstrated at 2 follow-up visits (Days 56 and 85 post last dose) and these 2 samples had neutralizing antibody activity. Of the 13 subjects that discontinued from the study and were analyzed for the presence of anti-abatacept and anti-CTLA4-T antibodies, no subjects were positive for the anti-abatacept antibody response and 1 (7.7%) subject was positive for the anti-CTLA4-T antibody response.

A relationship between immunogenicity and safety or efficacy was not apparent in subjects who developed a positive immune response to abatacept or CTLA4-T. The frequency and type of pre-

specified infusional AEs, overall AEs (serious and non-serious), and discontinuations were examined in subjects who developed an antibody response as well as for the subject who had neutralizing antibodies. The effect of immunogenicity on efficacy was also examined by evaluating DAS-28 CRP response, ACR responses, and HAQ responses in subjects with a positive antibody response. Interpretation of these data is limited due to the small number of immunopositive subjects.

- Rheumatoid Factor and Anti-CCP2

Serum samples were collected to measure RF and anti-CCP2 levels at screening and Month 6 and 12. All subjects randomized in this study had to have at least 1 of the 2 serologic tests positive. The number of subjects who seroconverted (were positive at baseline and negative at Days 169 and 365, or vice versa) was examined. More subjects treated with ABA + MTX (17.0% and 18.5%, respectively) had a positive to negative seroconversion of RF from baseline to Days 169 and 365 compared with subjects treated with PLA + MTX (9.5% and 14.6%, respectively). A greater proportion of subjects treated with PLA + MTX (14.3% and 16.7%, respectively) had a negative to positive seroconversion of RF from baseline to Days 169 and 365 compared with no subjects in the ABA + MTX group.

For anti-CCP2, more subjects treated with ABA + MTX (6.6% and 7.1%, respectively) had a positive to negative seroconversion from baseline to Days 169 and 365 compared with subjects treated with PLA + MTX (2.9% and 4.5%, respectively). A greater proportion of subjects treated with PLA + MTX (6.1% and 13.8%, respectively) had a negative to positive seroconversion of anti-CCP2 from baseline to Days 169 and 365 compared with no subjects in the ABA + MTX group. Treatment with ABA + MTX resulted in a greater reduction from baseline in anti-CCP2 measures compared with PLA + MTX. Reductions from baseline were seen by Month 6 and continued to be observed at Month 12. RF levels were reduced to a greater degree in the PLA + MTX group compared with the ABA + MTX group at Days 169 and 365.

Other Safety Studies

In addition to the safety data from the short term period of study IM101023 presented above, data from long term follow up from the following studies were submitted.

- **IM101023LT (ad 2-year follow up) Two year follow up of the Phase 3, multi-centre, randomized, double-blind study to evaluate remission and joint damage progression in methotrexate-naïve early, erosive rheumatoid arthritis subjects with abatacept plus methotrexate compared with methotrexate**

This addendum reports the efficacy, safety, and immunogenicity results for subjects who continued in the open-label period of the study (Year 2). This includes subjects in the original abatacept in combination with MTX group (ABA + MTX) who continued this treatment for an additional 12 months and subjects in the original placebo in combination with MTX group (PLA + MTX) who added abatacept in place of placebo for the open-label period (12 months).

The primary objective of the open-label period was to assess the long-term safety and tolerability of abatacept in subjects with early, erosive RA, including evaluation of immunogenicity.

Given the uncontrolled, open-label nature of this study, there are inherent limitations to interpreting the results, however, the high retention of subjects in the open-label period of this study allows greater confidence in the robustness of the results.

Abatacept treatment at a weight-tiered dose of 10 mg/kg (IV) administered every 28 days in combination with MTX for an additional 12 months in the open-label period after the 12-month double-blind period was generally well tolerated in subjects with early (≤ 2 years), erosive, seropositive RA, and similar to the first 12-month controlled period.

With regard to efficacy information on this trial the CHMP noted that:

Improvements in signs and symptoms (as assessed by DAS 28 and ACR responses) and health related outcomes (as assessed by SF-36, reduction of fatigue [VAS], and activity limitation), observed with abatacept treatment in combination with MTX at the end of Month 12 was maintained at the end of open-label period (Month 24) in the original abatacept in combination with MTX group; improvements were observed for the original placebo in combination with MTX group when treatment with abatacept in place of placebo was initiated during the open-label period. ACR responses were assessed at 2 years in 232 patients with 85% ACR 20 responses, 74% ACR 50 responses, and 54% ACR 70 responses.

Radiographic assessment indicated joint protection following 24 months of abatacept treatment in combination with MTX with less progression of structural damage at Month 24 relative to treatment for only 12 months. Early treatment with the combination of abatacept and MTX gave an additional benefit in protecting joint damage over starting with the standard of care of MTX only. Among the patients who entered the open-label 12 month period, 59% (125/213) of patients receiving continuous abatacept plus methotrexate treatment and 48% (92/192) of patients who initially received methotrexate and switched to combination with abatacept had no progression.

No new or unusual AEs emerged during abatacept treatment in the open-label follow up periods. Evaluation of laboratory data revealed no clinically significant trends or safety concerns. The overall incidence rates for SAEs, Infections and Infestations SOC SAEs, Infections and Infestations SOC AEs, malignant neoplasms, and autoimmune disorders did not increase during the open-label period relative to the double-blind period.

- **Long term follow up IM101102LT A Phase 3, multi-centre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of abatacept in combination therapy with methotrexate (MTX) vs. MTX alone in subjects with active rheumatoid arthritis and inadequate response to MTX. Clinical phase 3**

The primary objective of the open-label period was to assess the safety and long-term tolerability of abatacept in subjects who completed the 12-month, double-blind treatment period.

Abatacept at a weight-tiered dose of 10 mg/kg (IV) administered monthly for up to 6 years (up to 5 years in open-label period after 1-year double-blind period) was generally well tolerated in subjects with RA.

With regard to efficacy information on this trial the CHMP noted that:

Abatacept was effective in improving the signs and symptoms of RA, physical function, and quality of life, and these improvements were maintained during the open-label period. ACR responses were assessed at 5 years in 270 patients with 84% ACR 20 responses, 61% ACR 50 responses, and 40% ACR 70 responses.

When Erosion, JSN, and Total scores were analyzed by mean change in score from the previous annual visit, there was less progression of structural damage in subjects treated with abatacept for the entire open-label treatment period relative to subjects initially treated with placebo for 1 year and then treated with abatacept. By Year 5, the structural damage progression of the original placebo group, as measured by the annual change in Total score from the previous year, was similar to that observed in the original abatacept group. Data were analyzed using mean change in total score from the previous annual visit. The mean change was, 0.41 and 0.74 from year 1 to year 2 (n=290, 130), 0.37 and 0.68 from year 2 to year 3 (n=293, 130), 0.34 and 0.43 year from 3 to year 4 (n=290, 128) and the change was 0.26 and 0.29 (n=233, 114) from year 4 to year 5 for patients originally randomized to abatacept + MTX and placebo + MTX respectively.

No new safety concerns evolved in the 5 years follow up period and during this period the monthly abatacept dose was generally well tolerated by patients with RA. No new or unexpected AEs emerged during abatacept treatment in the open-label period. Evaluation of laboratory data revealed no clinically significant trends or safety concerns. The overall incidence rates for SAEs, Infections and Infestations SOC SAEs, Infections and Infestations SOC AEs, malignant neoplasms, and autoimmune disorders did not increase during the open-label period relative to the double-blind period. Efficacy outcomes were durable and sustained.

- **IM101100LT A Phase 2B, multi-centre, randomized, double-blind, placebo-controlled study to evaluate the safety and clinical efficacy of two different doses of BMS-188667 administered intravenously to subjects with active rheumatoid arthritis while receiving methotrexate Clinical phase 2B**

The primary objective of the long-term extension phase was to assess the safety and tolerability of abatacept combined with methotrexate (MTX) during long-term administration in subjects with active RA.

Abatacept at a weight-tiered dose of 10 mg/kg (IV) administered monthly over 7 years including the double-blind period was generally safe and well tolerated in subjects with RA. ACR responses were assessed at 7 years in 43 patients with 72% ACR 20 responses, 58% ACR 50 responses, and 44% ACR 70 responses.

- **Long term follow up IM101043LT of Phase 3, Multi-Centre, Randomized, Double-Blind, Placebo-Controlled Comparative Study of Abatacept or Infliximab in Combination with Methotrexate in Controlling Disease Activity in Subjects with Rheumatoid Arthritis Having an Inadequate Clinical Response to Methotrexate Clinical phase 3**

The primary objective of the long-term extension phase was to assess the safety and long-term tolerability of abatacept in subjects who had completed the initial 12-month double-blind treatment period.

Long-term treatment with abatacept for up to 44 months (open-label and double-blind periods) was generally safe and well tolerated in subjects with RA initially showing an inadequate response to MTX. No safety concerns were identified in the open-label period. The improvements in signs and symptoms of RA, physical function, and quality of life observed in subjects receiving double-blind abatacept were maintained over the 1 year of continued abatacept treatment in the open-label period. There was no evidence of a greater risk in terms of infections, infusional events, or SAEs associated with transitioning subjects directly from infliximab to abatacept, and efficacy was increased after subjects were switched from infliximab to abatacept.

This open label period of the study provided an assessment of the ability of abatacept to maintain efficacy for subjects originally randomized to abatacept and the efficacy response of those subjects who were switched to abatacept following treatment with infliximab. The reduction from baseline in mean DAS28 score at day 365 (-3.06) was maintained through day 729 (-3.34) in those patients who continued with abatacept. In those patients who initially received infliximab and then switched to abatacept, the reduction in the mean DAS28 score from baseline was 3.29 at day 729 and 2.48 at day 365.

- **Clinical Study Report Addendum 2008 for IM101029 A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and**

Safety of Abatacept vs. Placebo in Subjects with Active Rheumatoid Arthritis on Background DMARDs who have Failed Anti-TNF Therapy.

The primary objective of the open-label period is to assess the long-term safety and tolerability of abatacept combined with non-biologic background DMARDs in subjects with active RA.

Long term treatment with abatacept at a weight-tiered dose of 10 mg/kg (IV) administered monthly for up to 5 years after the 6-month double-blind period was generally safe and well tolerated in subjects with RA. Abatacept was effective in improving the signs and symptoms of RA, physical function, and quality of life during the double-blind period. These improvements were maintained during the open-label period. ACR responses were assessed at 5 years in 91 patients with 74% ACR 20 responses, 51% ACR 50 responses, and 23% ACR 70 responses.

- **Long term follow- up IM101031LT A Phase 3, multi-centre, randomized, double-blind, placebo-controlled clinical use study to evaluate the safety and tolerability of abatacept administered intravenously to subjects with active rheumatoid arthritis (RA), with or without medical co-morbidities, receiving disease modifying antirheumatic drugs (DMARDs) and/or biologics approved for RA (open-label period up to 31-Oct-2008) Clinical phase 3**

The primary objective of the open-label period was to assess the long-term safety and tolerability of abatacept in combination with approved background biologic and/or non-biologic DMARDs in subjects with RA who had completed the 12-month double-blind treatment period.

Abatacept, on the current recommended dose, administered monthly for 4 or more years after a 1 year period of double-blind therapy, had acceptable tolerance in a population of subjects with RA, with or without medical co-morbidities, who were receiving concomitant non-biologic disease-modifying RA therapies. However, concomitant therapy with abatacept and marketed biologic anti-rheumatic drugs was associated with an increase in adverse events, particularly infections.

- **Open-label Period of Study IM101101 A Phase IIb, Multicenter, Randomized, Double Blind, Placebo-Controlled Study to Evaluate the Safety and Clinical Efficacy of Intravenous Infusions of Abatacept (BMS 188667, 2 mg/kg) Given Monthly in Combination with Subcutaneous Injections of Etanercept (25 mg) Given Twice Weekly to Subjects with Active Rheumatoid Arthritis (Open-label Period)**

Assessment of the safety and tolerability of abatacept during long-term administration in subjects with active rheumatoid arthritis (RA).

Open-label abatacept administered monthly for up to 58 months after 12 months of treatment (at 2 mg/kg dose) in the double-blind phase was generally safe and well tolerated in subjects with active RA. The overall safety profile for abatacept during the open-label period was not different from that observed during the double-blind period. However, analysis of integrated safety data from other clinical studies involving abatacept indicated an increased number of SAEs and AEs, including infections, in subjects when using concomitant biologics, and for this reason, background biologic therapies for RA (including etanercept) were no longer permitted after Jun-2005. A low incidence of seropositivity for anti-abatacept antibodies was observed. The presence of antibodies to abatacept did not correlate with any clinical findings.

- *Post marketing experience*

The data provided on post marketing indicates that the safety profile of abatacept remains favourable in the currently licensed indication, is generally consistent with the safety profile observed in the clinical studies, and new or unexpected safety signals have emerged.

Discussion on Clinical Safety

The extensive risk management program for abatacept links several registries, post marketing and clinical trial experience. The majority of these patients were enrolled to these clinical trials after an insufficient response to one or more non biologic DMARDs including MTX. During the cumulative period, 1280 patients had an inadequate response to MTX, 1419 patients having previously failed one or more anti- TNF agents, and 483 patients were MTX-naive.

Since its initial approval in the EU with the abatacept indication limited to the anti-TNF failure population (third line indication), additional safety data have been collected from the long term extensions of the clinical trials, the established RA registries, and the standard post-marketing surveillance, totalling an exposure of approximately 73,882 patient-years (p-y) of exposure (11,657 p-y cumulative trial, ~ 2000 p-y from post-marketing epidemiology studies, and ~60,225 p-y post marketing pharmacovigilance). These safety data are not limited to the third line indication as abatacept is marketed in the United States and other countries with an indication for use in MTX-inadequate responders, as well as in MTX-naive patients (over 10000 patients in total). In total 4632 subjects have been exposed to abatacept in the context of clinical trials, mostly on the fixed weight tiered dose of 10 mg/kg across the current and the newly proposed indications, representing 12375 patient-years of cumulative short and long term exposure. In this population, the number of subjects exposed for at least 5 years exceeds a thousand. These numbers are sufficient to meet ICH recommendations, for all indications.

Overall, abatacept is well tolerated by most patients. No new, unexpected adverse events were detected in the long term follow up studies, the sole randomised controlled trial or in post marketing experience. Compared to the original application identified and potential risks have also been better characterised over time. The frequency of overall adverse events and serious adverse event were comparable over time. Considering the mode of action of abatacept, there are several potential risks associated with immunosuppression including infections, autoimmunity and malignancies. Infections remained the primary identified risk associated with the use of abatacept also during the long term. The incidence rate of infections did not, however, increase over time and serious and opportunistic infections were rare. Data on the long term use of abatacept did not suggest that the risk of malignancies as specifically increased and the rates remained stable over time.

According to current safety database, the safety profile of abatacept seems to be better than that of the TNF-inhibitors and rituximab. This is due to the lower occurrence of serious or other infections. T cell immunosuppression is known to increase the frequency of certain neoplams (e.g. skin and lymphoid system neoplasms), and this possibility cannot be excluded for abatacept although there is no signal in the current safety data base. According to the present data, a risk of PML has not been demonstrated. No *de novo* cases of PML have been detected. The current RMP is considered adequate for the detection of rare events and events with latency provided that the exposure and recruitment to the pharmacoepidemiological programme is adequate.

It is unfortunate, that data from the epidemiology/ registry studies in the RMP are not yet able to provide more definite answers to the different safety concerns. The full planned analysis of the pharmacoepidemiological data across the registries is not expected to start before 2011. The current extracted data is interim in nature and mainly from unadjusted analysis. As outlined in the RMP, once

there are 5000 p-y across all studies, these analyses will be performed, but these data will be available at the earliest 2011. Currently the exposure is approximately 2000 p-y of follow-up. Keeping these limitations in mind, when comparing key events between abatacept and control groups, the results appear reassuring. The current data do not raise signals of unexpected adverse reactions.

The clinical evidence of an increased risk of organ specific autoimmune diseases (including diabetes or autoimmune thyroiditis) with abatacept is scarce. No new safety findings that would raise concerns were evident in the long term follow up. As incidence of these diseases is very low, in spite of an increased background rate in RA patients, risk estimations are difficult to perform between therapies for which no clear increase in incidence rates have been declared. Post marketing surveillance has associated TNF-inhibitors with certain specific autoimmune diseases (such as autoimmune hepatitis type 1, aplastic anemia, vasculitis and exacerbation of SLE or a demyelinating disorder). The current case reports with abatacept do not suggest such causality to abatacept. For the time being, the data on autoimmunity from the pharmacoepidemiological programme are preliminary, fully analysed data will only be available in 2011.

Against this background, the RMP for abatacept has a paramount role as the monitoring of autoimmune events remains also an important part of the ongoing safety monitoring of abatacept. The risk management system is extensive, but assessment of autoimmunity remains challenging. To improve the evaluation of immunogenicity and its significance for possible autoimmune events, the MAH has agreed to follow-up the antibody response up to six months after cessation therapy. Immunogenicity will also be addressed upon detection of an autoimmune event. This is proposed (in addition to the JIA programme) for the adult SC programme, but should also be employed for other part of the adult development programme of abatacept. However, the utility of the paediatric biomarkers for thyroiditis and diabetes (anti-GAD and anti-TPO) in the different adult populations, with no definite signal, is not seen as relevant. The use of other biomarkers is considered questionable. The current RMP is adequate for the detection of rare events provided that the abatacept exposure and recruitment to the pharmacoepidemiological programme are adequate.

The methods used for the determination of the immunogenicity in these studies have been validated and the validation reports have previously been assessed by the CHMP and they are considered acceptable. In general, low immunogenicity was seen across all of the clinical studies. There was detectable variation between the different studies in the numbers of positive individuals, with the values shifting from 2% to 20%. To date, no associations of abatacept antibodies with infusion reactions, adverse events, decreased efficacy, or changes in drug concentration have been detected. The duration of the follow up is important also for autoimmune disorders as they are known to manifest clinically several years after the initial immunological insult. In order to cope with this problem, the MAH proposes to monitor abatacept antibodies in the SC programme.

3.3 Pharmacovigilance

Pharmacovigilance system and Risk Management plan

The currently approved RMP (version 8.0) addresses identified and potential risks in MTX IR and TNF IR patient populations. The clinical experience to date in MTX naive patients did not reveal any information or safety issues that would require changes to the identified and potential risks in the existing RMP. Therefore, the routine and enhanced pharmacovigilance measures that are established in the earlier RMP versions remain sufficient.

There is no need for revision to the RMP at this time based on the proposed extension of the therapeutic indication, but the MAH is required to update the RMP with the new exposure data at the time of the next RMP update. The MAH is required to include the following additional data/information

to the RMP at the time of the next RMP update: Safety Specifications and Clinical exposure to be updated with the data pertaining to this variation application (see Attachment 6 - LoU).

3.4 Benefit Risk Assessment

Benefits

The treatment paradigm of RA is changing towards more aggressive early intervention in order to quench the inflammation that may lead to irreversible joint damage and impaired function. Even in aggressive, erosive RA, it is possible to obtain a remission, not only relieve signs and symptoms. Results of the combination therapies, either with traditional DMARDs or with MTX + biologicals, such as abatacept, are significantly better than mono therapy with traditional DMARDs, including MTX. Study IM101023 demonstrated that abatacept + MTX provides a clinically significant benefit to patients with early RA in terms of disease activity, progression of the disease, physical function and quality of life as compared to placebo + MTX. These results are in line with previous studies in advanced RA. The clinical benefit of abatacept appears to be of a similar magnitude as that provided by etanercept, infliximab and adalimumab. Data on the long term benefits of biologicals are scarce and difficult to evaluate.

Uncertainty in the knowledge about the beneficial effects

The size of the radiological abatacept treatment effect, as measured by a validated clinical score, appeared, however, modest, although the statistical analysis on this outcome was not sensitive to the choice of the analyses method. Across-study comparisons are difficult in this area.

Risks

The tolerability of the combinations that include a biological medicinal product has been relatively good. The safety profile of the combinations with infliximab, adalimumab and etanercept is well known. The most significant serious adverse effects are related to immunosuppression/host defence and include opportunistic infections, lymphomas and various autoimmune disorders. The concerns on the long term safety of abatacept, such as risk of malignancies and autoimmune disorders, are more based on the novelty of the mode of action of abatacept and isolated clinical findings than on real reports of adverse effects in patients. Infections remain the primary identified risk associated with the use of abatacept also during the long term. The incidence rate of infections did not, however, increase over time and serious and opportunistic infections were rare. Data on the long term use of abatacept did not suggest that the risk of malignancies as specifically increased and the rates remained stable over time. Thus, abatacept may offer a relative safety benefit to patients who are susceptible for infections as compared to TNF-inhibitors. Confirmation on this point may come from the ongoing pharmacoepidemiological studies.

Because of these concerns, a robust risk management program was established for abatacept at the time of licensing. This extensive risk management program for abatacept links several registries, post marketing and clinical trial experience. The majority of these patients were enrolled after an insufficient response to one or more non biologic DMARDs including MTX. During the cumulative period, 1280 patients had an inadequate response to MTX, 1419 patients having previously failed one or more anti- TNF agents, and 483 patients were MTX-naive. Since its initial approval in the EU with the abatacept indication limited to the anti-TNF failure population (third line indication), additional safety data has been collected from the long term extensions of the clinical trials, the established RA registries, and the post-marketing experience, totalling an exposure of approximately 73,882 patient-years (p-y) of exposure (11,657 p-y cumulative trial, ~ 2000 p-y from post-marketing epidemiology studies, and ~60,225 p-y post marketing pharmacovigilance). These safety data are not limited to the third line indication as abatacept is marketed in the United States and other countries with an

indication for use in MTX-inadequate responders, as well as in MTX-naive patients (over 10000 patients in total).

Overall, abatacept is well tolerated by most patients. No new, unexpected adverse events have been detected in the long term follow up studies, the sole new randomised controlled trial or in post marketing experience. Compared to the original application, the identified and potential risks have also been better characterised over time. The frequency of overall adverse events and serious adverse event did not increase over time.

Unfavourable effects

Infections remain the primary identified risk associated with the use of abatacept also during the long term. The other concerns on the long term safety of abatacept, such as risk of malignancies and autoimmune disorders, are based on isolated clinical findings and novelty of the mechanism of action.

Uncertainty in the knowledge about the unfavourable effects

Abatacept has a comprehensive risk management plan that consists of extensions of clinical trials, pharmacoepidemiological study based of several RA registers as well as immunological studies and standard post-marketing safety surveillance. It is unfortunate, that data from the epidemiology/ registry studies in the RMP are not yet able to provide more definite answers to the different safety concerns in early RA. The full planned analysis of the pharmacoepidemiological data across the registries is not expected to start before 2011. The current extracted data are interim in nature and mainly from unadjusted analysis. As outlined in the RMP, once there are 5000 p-y across all studies, these analyses will be performed, but these data will available at the earliest 2011. Currently the exposure is approximately 2000 p-y of follow-up. Keeping these limitations in mind, when comparing key events between abatacept and control groups, the results appear reassuring. The current data do not raise any new safety signals.

Benefit-risk balance

Clinically significant benefits of abatacept have been demonstrated both in early and advanced RA. As discussed above, the mode of action of abatacept raises some potential risks. Against this background, the RMP has a paramount role in the ongoing safety monitoring of abatacept. The risk management system is extensive and on the basis of the current know safety data, with no clear new safety signals, it is considered adequate (with an update on post treatment follow-up of immunogenicity), also for the detection of rare events and events with latency, provided that the exposure and recruitment to the pharmacoepidemiological programme is adequate.

Discussion on the benefit-risk assessment

It is generally accepted that the combination of MTX with a biological is more active than methotrexate (MTX) alone and this appears true also for the abatacept-MTX combination. It is acknowledged that the study submitted in this application in support of the initially claimed indication in the MTX naïve population has provided data on clinically significant short term benefits. It can be seen that the different trials in early RA (abatacept and anti-TNF) are also similar in their design and results. The size of the radiological abatacept treatment effect appeared, however, small and comparisons to other therapies cannot be fully estimated on the basis of this submission, which would argue against the use of abatacept as first-line monotherapy. In the absence of a head-to-head comparison to a TNF inhibitor, there is some uncertainty of the relative benefits as compared to TNF inhibitors. For the time being, the safety data have not revealed clear safety signals other than increased susceptibility to infections. On the basis of a quite sizable safety data base, abatacept appears to lack some adverse effects associated with TNF-inhibitors. Thus, the relative benefit/risk of abatacept and TNF-inhibitors, especially in the long term, remains somewhat uncertain. Therefore, an application for a first line

indication (or the use of abatacept as monotherapy in case of methotrexate intolerance) is considered premature, which was accepted by the MAH.

However, based on the available evidence and particularly the safety data generated since the original licensure the CHMP recommends that abatacept is placed into the second line for patients who have responded inadequately to one or more DMARDs or TNF-inhibitors. In these patients, the benefits outweigh the potential risks. Hence, the proposed therapeutic indication is as follows:

"ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonist.

Conclusion

The overall B/R of is positive for the following indication with rewording (**bold**- addition of text; ~~strikethrough~~-deletion of text):

"ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who ~~have had an insufficient response or intolerance~~ **responded inadequately** to ~~other~~ **previous therapy with one or more** disease-modifying anti-rheumatic drugs (DMARDs) including ~~at least one tumour necrosis factor~~ **methotrexate (MTX) or a** TNF-alpha inhibitor."

4. Conclusion

On 20 May 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.