SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Humira. For information on changes after 1 October 2003 please refer to module 8.

1. Introduction

Rheumatoid arthritis (RA) is a common, chronic, inflammatory disorder of the joints predominantly affecting young adults and premenopausal women. The disease is characterized by a progressive inflammatory synovitis manifested by polyarticular joint swelling and tenderness. The synovitis results in erosion of articular cartilage and marginal bone with subsequent joint destruction. This bony destruction is thought to be irreversible. There is no known cure for RA.

Rheumatoid arthritis produces substantial morbidity and increased mortality. Specifically, pain, swelling and stiffness in multiple joints is the hallmark of the disease. Analgesics are usually required on a chronic basis. Within 2 years of diagnosis, patients usually experience moderate disability; and after 10 years 30% are severely disabled. In addition to loss of employment, this disability often compromises the ability of patients to undertake their activities of daily living and can impact sexual and social functioning.

Cytokines, hormone-like proteins that allow cells to communicate, play critical roles in normal biologic processes, such as cell growth, inflammation and immunity. Two inflammatory cytokines, tumor necrosis factor (TNF) and interleukin-1 (IL-1), are critical in the progression of inflammatory synovitis and articular matrix degradation, and therefore represent promising targets for therapeutic intervention in RA. Clinical experience with agents that block TNF activity demonstrate the central role for this cytokine in the pathogenesis of RA and other autoimmune diseases
Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Humira is indicated for:
"the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.

To ensure maximum efficacy, Humira is given in combination with methotrexate. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate."

The recommended dose of adalimumab for adult patients with rheumatoid arthritis is 40 mg (per 0.8 ml, in a vial or prefilled syringe) given every other week as a subcutaneous injection. Methotrexate (MTX), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with adalimumab.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Humira is presented as a vial, or a single-use prefilled syringe, containing 40 mg of active substance in 0.8 ml of a buffered solution comprised of mannitol, citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, and Polysorbate 80. The container is a type I glass vial with a rubber stopper or a pefilled syringe composed of type I glass with an integrated needle and rubber plunger.

Development pharmaceutics

Studies conducted for optimisation of the commercial formulation included accelerated stability to demonstrate that a 50 mg/ml concentration formulated with phosphate and citrate buffers provides sufficient chemical stability at an acceptable pH for injection. Mannitol and sodium chloride were added to achieve the correct tonicity.The amount of Polysorbate 80 was optimized to minimise the formation of aggregates, as well as sub-visible and visible particles during agitated and freeze-thaw conditions.

Active substance

The active substance is adalimumab, a recombinant monoclonal antibody directed to human TNF-α. Adalimumab is an IgG antibody composed of two kappa light chains each with a molecular weight of approximately 24 kDa and two $IgG1^{z, a}$ heavy chains each with a molecular weight of approximately 49 kDa. The total molecular weight of adulimumab is 148 kDa. Each light chain consists of 214 amino acid residues and each heavy chain consists of 451 amino acid residues.

Development Genetics

Adalimumab can be considered "fully human" in the sense that the coding gene sequences contain no elements cloned from any other species.

Data on the isolation and maturation of the human sequences and on the construction and verification of the expression vector are well described and are acceptable.

The expression vector contains sequences for the variable regions obtained via phage display library methodology and sequences containing the human IgG constant domains. The nucleotide sequences of the final expression vector was confirmed by DNA sequencing.

The stable integration of the transfected sequences in the production cell line was concluded from the analyses of the number of integration sites (Southern Blot), copy number (Southern Blot), mRNA size (Northern Blot) and the integrity of the coding sequences (cDNA sequencing). These tests were performed on cells from the MCB and on Post Production Cells. WCB testing included the analysis of mRNA and copy number.

Cell Bank System

A clone adapted to growth under serum-free conditions was used for establishment of the Master Cell Bank.
The preparation, storage and safety testing of the MCB, WCB and PPCB are adequately described. Two WCB's have been prepared. For the establishment or storage of the second WCB no animal derived raw materials were used. Information on the preparation, control and characterisation of cell banks to be used in commercial production has been given.

Production of the active substance

The active substance is manufactured by Abbott Bioresearch Center, Worcester, MA, USA.
Cell culture

The active ingredient is produced by cell culture using Chinese Hamster Ovary (CHO) cells in media with no human or animal derived components. Expansion of the CHO cell culture from a single vial of the WCB is accomplished by sub-cloning into spinner flasks of increasing size. When reaching a suitable level for inoculation, cells are transferred to the seed fermentor for the final expansion before seeding the production bioreactor. After an additional cultivation, production medium is added to increase the culture volume to final batch size.

Descriptions are provided of each fermentation step and the in-process control tests performed are listed along with their limits set for specification. Holding times of intermediates, operation parameters and quality of raw materials are adequately defined. The description provided on the working facilities as well as of the procedures for preparation of buffers and media is satisfactory.

Purification

Adalimumab is purified through several chromatography steps and is subject to low pH treatment and nanofiltration for virus inactivation/removal.

Descriptions are provided of each individual step and the in-process control tests carried out throughout purification are listed along with their limits set for specification. Representative elution profiles are shown. The range in operation parameters for each step is defined and conditions used for regeneration/storage of columns are specified. Procedures for the preparation and control of buffers are adequate.

Characterisation of the active substance

Extensive physico-chemical tests and biological and immunological studies have been performed to characterise adalimumab.

As seen for other recombinant antibodies, adalimumab is present in three major forms, corresponding to molecules carrying two, one or no C-terminal lysine. In adalimumab preparationsthese three main components constitute only around 85% of the material. The rest, representing approx. 15 % of the active substance, elutes as a number of poorly resolved peaks in the ion exchange HPLC assay.

Although these more acidic species have been isolated from the three major forms of the antibody and subjected to extensive characterisation using state-of-the-art techniques, it has not been possible to correlate the shift in mobility to changes in the antibody structure. Since these species cannot be resolved by traditional analytical methods e.g. SDS PAGE it is likely that the structural differences are minor, with no influence shown on TNF-α binding in *in vitro* model systems. The fermentation step is critical for the formation of the acidic species and an in-process control has been set at this stage. The separation for quantification into regions based on their relative retention time in the WCX-analysis constitutes an acceptable means of controlling these species in release specifications and for monitoring the stability of the product.

The applicant has committed to perform post-licensing studies to map structural changes involved in the temperature-dependent conversion of the Lys-0, Lys-1, and Lys-2 forms of the adalimumab into the more acidic species in the WCX-10 analysis. Based on this information, structural differences and similarities between degradation products and the acidic species formed during fermentation will be identified.

The monitoring of product-related impurities that may arise in production or storage of the drug substance performed on a routine basis is considered acceptable.

In conclusion, taking into account the consistency of levels of acidic species during fermentation, the in-process controls during fermentation and the quantitative control of the acidic species during release testing of the active substance, the CPMP considered that the proposed specification for testing of the active substances are adequate.

Stability of the active substance

Based on the applicant's presented data, a shelf life of 18 months for active substance stored at -80 °C or between -20 to -25 °C is supported.

Other ingredients

All excipients used for the formulation of the product in pre-filled syringes or in vials are tested for compliance with Ph.Eur monographs. Certificates of analysis for each component have been provided.

Product development and finished product

Manufacturing Process

Manufacture of the finished product is performed at Vetter Pharma-Fertigung, GmbH, Ravensburg, Germany and Dr. Madaus GmbH, in Wasserburg, Germany. Filled syringes and vials are labelled and packaged by Vetter Pharma-Fertigung, GmbH, Ravensburg Germany.

Excipients are introduced in the active substance manufacturing process by diafiltration in the last step before filling of the bulk. Manufacturing of finished product includes dilution of the bulk active substance with an identical solution of excipients to achieve the target active concentration of 50 mg/ml. This is followed by sterile filtration, aseptic dispensing and closure in pre-sterilised type I glass syringes or vials in a controlled environment. Both processes use standard sterile filtration and filling unit operations under controlled conditions with in process controls including holding time prior to filtration, filter integrity and fill weight.

Validation of the process

The validation of the manufacturing process for drug product is based on extended in process test control during commercial scale production of four batches of pre-filled syringes (Vetter Pharma-Fertigung, GmbH) and three batches of vials (Dr. Madaus GmbH). The in process testing included control of critical steps such as mixing and microbial control as well as product purity and biological activity over the defined maximum time duration in manufacture.

The studies for validation of the manufacturing process are well designed and reported. All deviations to the protocols are discussed in separate sections, and in most cases, the corrective actions appear well funded.

Finished product specifications (batch release and shelf-life)

Analytical methods used for the release control and for the monitoring of the stability of drug product are satisfactorily validated. All batches analysed met all specifications set for release of finished product. Historical batch data are provided to support both product presentations.

Stability tests on the finished product

The data presented for each presentations are consistent and confirm the stability of the finished product and support the proposed shelf life of 18 months, storage at 2-8 °C.

Viral Safety

No animal derived materials are used in the manufacture of adalimumab for commercial distribution. Primatone RL derived from bovine sources and amino acids from human hair, poultry feathers and bovine/porcine sources were used in the preparation of the MCB and the first WCB. Satisfactory information has been provided to demonstrate the TSE compliance. For the preparation of the second WCB and for commercial production only material derived from bacteria, yeast or soybeans will be used. The recombinant insulin used as additive to the tissue culture media is registered in its final dosage form in the US.

The testing performed for safety control of the MCB and PPCB included species-specific virus assays (MAP with LCM challenge, HAP), in vitro virus assays, in vivo virus assays, bovine virus screen, retroviruses, transmission electron microscopy (TEM), reverse transcriptase, co-cultivation with mink

lung cells, co-cultivation with human RD cells, mycoplasma, sterility, and isoenzyme analysis. Non-infectious Type A retroviral particles were observed, as is typical for CHO cells. No other evidence of microbial or viral contamination was found. Safety testing of the WCB was less extensive and included species-specific virus assays (MAP with LCM challenge, HAP), in vitro virus assays, mycoplasma, sterility, and isoenzyme analysis. No evidence of microbial or viral contamination was found. Results from the safety testing of the cell banks are presented.

Every lot of unprocessed bulk harvest is tested for the presence of virus and includes species-specific virus assays (HAP, MAP with LCM challenge), in vitro virus assays, transmission electron microscopy (TEM), mycoplasma, sterility, and Q-PCR for MVM. The studies demonstrating specificity, sensitivity and robustness of the MVM PCR method have been provided.

Scaled-down models of process steps were used for validation of virus removal/inactivation. The validation studies are generally well performed. Calculations of the reduction factor have been done according to recommendations in the EU guideline. As expected the purification process showed a limited clearance values for small non-enveloped virus such as MVM.

Therefore, each harvest will be tested for the presence of viruses and a specific assay (Q-PCR) has been introduced to detect MVM.

Discussion on chemical, pharmaceutical and biological aspects

Humira is presented as a single-use prefilled syringe, or a vial, containing 40 mg of active substance in 0.8 ml of a citrate/phosphate buffered solution. The formulation also contains Polysorbate 80.

The active substance is adalimumab, a recombinant monoclonal antibody directed to human TNF-α. Adalimumab is an IgG antibody composed of two kappa light chains each with a molecular weight of approximately 24 kDa and two $IgG1^{z, a}$ heavy chains each with a molecular weight of approximately 49 kDa for a total molecular weight of 148 kDa.

The manufacturing process of both the active substance and the finished products is generally well described and adequately controlled. The results show consistency of the manufacturing process. Appropriate specifications have been set to control the active substance and finished product, both at release and at the end-of-shelf life. A shelf life has been agreed of 18 months at –80°C and –20°C for the active substance, and of 18 months at 2-8°C for the finished product.

The characterisation studies of the active substance showed the presence of approx. 15 % of acidic species. The fact that the acidic species have not been fully characterised was not considered by the CPMP as a major shortcoming to the quality part of the dossier or to the quality of the product for the following reasons:
- Historical batch data showed that there are no significant differences in the total amount of acidic peak material between batches from commercial production and those used in the clinical trials;
- Consistency of production of these acidic species during the fermentation is controlled by in-process controls;
- Consistency of acidic species in the active substance is controlled by routine release tests.

The capacity of the production process to eliminate/inactive viruses has been presented. Each harvest will be tested for the presence of viruses and a Q-PCR assay has been introduced to detect MVM. No animal derived materials are used in the manufacture of adalimumab for commercial production. Satisfactory information has been provided to demonstrate TSE compliance for the materials of ruminant origin used during the production of the MCB or WCB.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

- *In vitro* and *in vivo* studies

Binding of adalimumab to soluble recombinant human (rh)TNFα was saturable and concentration-dependent (Kd 5.8 – 8.7 10^{-11}). Binding to pro-TNFα (transmembrane TNFα), was also demonstrated. Additional *in vitro* studies showed that adalimumab inhibited the binding of rhTNFα to both TNFα receptors (p55 and p75; IC_{50} 10^{-9} -10^{-10}M). It also inhibited hTNFα-induced expression of adhesion molecules (IC_{50} 1-2 10^{-10}M). Specificity of adalimumab for rhTNFα was supported by demonstrating binding to human TNFα, but not human TNFβ and a number of different cytokines. *In vitro*, adalimumab bound to Fc receptors of human cells, indicating that the immunoglobulin effector functions of adalimumab were intact.

In vitro, adalimumab is a potent inhibitor of TNFα from human, various primates including cynomolgus monkey, and dog (IC_{50}s 10^{-10} –10^{-11} M). Neutralisation of murine TNFα was considerably weaker (>2.0 x 10^{-7}), and adalimumab did not bind rat TNFα. However, in vitro assays revealed staining of structures in the cytoplasm of vascular smooth muscle in human tissues but not in tissues from cynomolgus monkey, which somewhat limits of the monkey as a model for human safety assessment. Due to the low affinity for mouse TNFα as well as the rapid development of murine anti-human antibodies [MAHA], the relevance of mouse as a species for human safety assessment is considered low.

Using fresh animal complement source, adalimumab induced lysis of transfected cells over-expressing pro- TNFα. Whether this has any relevance *in vivo* is unknown. No complement –related tissue injuries have been seen in the animal studies, which provides some reassurance. In a pharmacology study in the Tg5453 mouse model (expressing a transgene that encodes human pro-TNFα) adalimumab derived variants with and without effector functions were equally potent. However, the ability to activate human complement has not been studied. The relevance of these data for humans with RA is unknown.

In vivo, adalimumab inhibited hTNFα-induced lethality in D-galactosamine sensitised mice and hTNFα-induced pyrexia in rabbits. Moreover, it prevented development of arthritis in two transgenic mouse models, the Tg197 (expressing a soluble human TNFα transgene) and Tg5453 (expressing a transgene that encodes human pro-TNFα), serving as disease models of polyarthritis. ED_{50} values were in between 0.1-0.5 mg/kg.

- General and safety pharmacology programme

A number of general pharmacology/safety pharmacology studies were performed focussing on the CNS, cardiovascular system, GI tract, renal function, female uterus, local anaesthesia, and *in vitro* studies with human blood. Several of these used rats/rat tissues, or guinea pig /tissues. Since adalimumab did not bind rat TNFα, and there are no data on the affinity of adalimumab for guinea pig TNFα, these studies are of limited value. The studies in dogs (CV effects) and with human blood are considered more relevant. There were no findings in these studies that raise any clinical concerns.

- Pharmacodynamic drug interactions

No specific studies were performed.

Pharmacokinetics

Analyses of adalimumab and of anti-adalimumab antibodies (MAHA or primate anti human antibodies [PAHA]) were made by ELISAs. These methods were adequately validated, and demonstrated to be sensitive and specific. However, these assays can only detect free adalimumab or free, non-complexed MAHA/PAHA. Thus, presence of adalimumab interfered with the analyses of

MAHA/PAHA; and vice versa. These assay limitations reduce the reliability of the pharmacokinetic data and the possibility to assess systemic exposure in the toxicity studies.

Conventional studies addressing protein binding, metabolism or excretion of adalimumab were not performed. The lack of such studies is acceptable for this type of compound. Placental transfer was demonstrated in the developmental study in monkeys.

Data from *in vitro* human tissue binding studies showed that adalimumab stained with filamentous structures in the cytoplasm of vascular smooth muscle and of other cells with contractile properties, in a number of tissues. Further investigations indicated that the staining could be reduced by human TNF or human serum. The Applicant has provided limited support that under physiological conditions the cytoplasm would not be accessible, and that no staining was observed in any structure of any human tissue that would be accessible to circulating therapeutic antibodies. Thus, the in vivo relevance of this finding is uncertain.

In mice and monkeys, the pharmacokinetics of adalimumab were linear as long as anti-adalimumab antibodies were absent. However, both MAHA and PAHA developed after single doses, and affected the elimination. Moreover, analyses of biological activity of serum samples showed that PAHA were neutralising. Thus, parameters such as clearance and half-life could not be determined with certainty. In general though, elimination was slow in both species ($t_{1/2}$ about 14 –21 days in monkeys).

Toxicology

The toxicology program included studies of single and repeat dose toxicity, genotoxicity, developmental toxicity and local tolerance. Adalimimab was generally administered via the i.v. route, while the intended clinical route is s.c. administration. This is not considered to hamper the assessment of toxicity.

- *Single dose toxicity:*

The data derived from studies performed in mice and rats after i.v. administration show that in rodents, a single dose of Adalimumab appears to be well tolerated up to a dose of almost 2000 times higher than the single human dose, the target organ of toxicity in rat was the spleen.

- *Repeat dose toxicity:*

The studies in *cynomolgus monkeys* are considered most relevant for human safety assessment. Repeat dose toxicity studies of 4 weeks (32 – 157 mg/kg bw) and 39 weeks (32- 215 mg/kg bw) duration were performed. Overall, no major toxicological concerns were identified. As expected, TNFα inhibition resulted in effects on organs of the immune system, including thymus (decreased weight, involution, reduced lymphocytes, cystic transformation) and spleen (reduced activation and cellularity of the follicular centre). Immunohistochemical analyses confirmed effects on various immune cells in these organs. In the 39 weeks study, most of these changes were reversible within the 20-week recovery period. In this study, the NOAEL was 32 mg/kg, with an AUC of 304 800 µg*h/ml.

There is a vast amount of published literature from preclinical models that demonstrates the role of TNFα in the protective immune responses against various infective agents. There are also data showing that administration of anti-TNFα monoclonal antibodies reduced host defence, which in a number of cases lead to enhancement of infection-induced mortality. The clinical experience with authorised anti-TNF therapies clearly confirms a reduced defence against infections as the main adverse effect of such treatment.

After 39 but not 4 weeks, deposition of immune complexes, was observed in isolated glomeruli in the kidneys of most animals give 215 mg/kg bw. There were no inflammatory reactions, or functional changes observed in association with these deposits.

One problem has been identified. In both the 4 and 39 weeks primate studies, low levels of adalimumab were detected in control monkeys. PAHA analyses from samples in the 4 weeks study revealed PAHAs in 7 out of 10 controls. Despite careful investigation no evident reason for

contamination has been identified; several measures to reassure adequate conduct of the study had been taken. The explanation of the possible contamination may be plausible.

The available toxicokinetic data show exposure of animals to adalimumab during the toxicity studies, in considerable excess of humans given intended therapy. Development of PAHAs could not be determined in these animals due to assay limitations, but cannot be excluded. However, high concentrations of adalimumab were detected in samples from treated animals throughout the study, which support that PAHAs had not markedly neutralised the adalimumab activity during the study.

- *Genotoxicity:*

The *genotoxic* potential of adalimumab was tested in vitro by gene mutations in bacteria and in vivo in the mouse micronucleus test. No genotoxic effects were seen. This is not a complete genotoxicity test battery (see CPMP/ICH/174/95, S2B). However, for a monoclonal antibody, genotoxicity tests are considered to be of limited value and are therefore not needed (CPMP/ICH/302/95, S6).

- *Carcinogenicity:*

No carcinogenicity study was performed with adalimumab. The lack of such studies is justified because there is no conventional or alternative model available, (i.e adalimumab has low/no affinity for mouse/rat TNFα, and MAHA developed after single doses). Adalimumab had no genotoxic effects, and no atypical tissue changes were seen in the 39 weeks monkey study. It is agreed that there is no indication of a direct carcinogenic effect of an anti-TNFα antibody. However, the consequences of long-term immunosuppression are unknown and an increased risk of a poorer control of nascent tumours cannot be ruled out. The lack of carcinogenicity studies has been reflected in the SPC.

- *Reproduction Toxicity:*

Effects on male fertility have not been studied. In females, no study beyond the developmental toxicity study in cynomolgus monkey has been performed. Generally, fertility studies are performed in rodents. However, neither the rat nor the mouse is considered as particularly relevant models for human safety assessment. The human tissue cross-reactivity studies and the histopathological evaluation of male and female reproductive organs in the repeat dose toxicity studies in monkeys revealed no cause for concern. Whether long-term inhibition of TNFα will affect fertility is not known.

One developmental/prenatal toxicity study was performed in *cynomolgus* monkeys (30 or 100 mg/kg/w, days 20-97 *post coitum)*. Caesarean section was performed day 100. Other females were allowed to deliver and the infants were observed for 1 week. There were no treatment related effects on the maternal animals, gestation, parturition, on fetuses or on the infants.
Available data showed that fetuses were exposed to adalimimab, corresponding to 5-10% of the maternal serum levels. Levels in amniotic fluid were 4-17 fold lower than the fetal levels. PAHAs were not measured. Taken together, these data are not sufficient to support the safe use of adalimumab in pregnant women.

The risk of use of adalimumab in pregnant women is unknown. Based on a large amount of published data, it is evident that TNFα is involved in embryonic development. For instance, although homozygous TNFα deficient mice were viable, fertile and developed normally but the immune function of these mice was compromised, and they were highly susceptible to challenges with infections agents. Thus, inhibition of TNFα may affect the development of the embryo and/ or fetus. Thus, adalimumab should not be used during pregnancy. Due to the slow elimination of adalimumab, pregnancy should be avoided for an extended period of time after finalisation of treatment.

Excretion of adalimumab in breast milk has not been studied in either animals or humans. However a time period during which pregnancy and breast feeding should be avoided has been proposed to be 5 months, based on the population PK parameters and their variability, as well as the longest individual half-life observed.

- *Local Tolerance:*

In rabbits, no local intolerance was seen after administration of the formulation intended for marketing. Moreover, no effects at the injection sites (after both i.v. or s.c.) were seen in various studies in monkeys.

4. Part IV: Clinical aspects[1]

Clinical pharmacology

Pharmacodynamics

- Mechanism of action

Pharmacodynamic effects expected of a TNF antagonist were shown in *in vitro* and *in vivo* preclinical studies. In patients, effects on relevant cytokines (IL-6 and TNF) were demonstrated, which were qualitatively similar to those noted for other TNF antagonists. A serum adalimumab – effect relationship could be established for relevant parameters of disease symptoms and signs. Table 1 summarises the clinical pharmacology studies.

Pharmacokinetics

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (V_{ss}) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Dose and time dependencies

The pharmacokinetics of adalimumab are essentially linear, although small deviations occur at higher doses than suggested for clinical use.

Presence of anti-adalimumab antibodies (AAA) and the effect of AAA on the pharmacokinetics of adalimumab

The frequency of AAA positive samples was quite variable among the pharmacokinetic studies (from almost zero up to 33% in a study in healthy volunteers). The variability may be partly due to the fact that there is interference by adalimumab with the antibody analysis.

The median CL/F (apparent clearance) was 59 and 17 ml/h in patients with and without AAA, respectively. This may be a true effect, but the results could also be due to assay artefacts caused by possible interference by AAA in the adalimumab analysis.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Populations at risk

The pharmacokinetics of adalimumab have not been studied in patients with significant hepatic or renal impairment. There is a trend to decreasing CL with increasing age. No gender differences have been observed.

[1] A Glossary for this section is available at the end of the text

Interactions

In general, interactions with antibodies are difficult to predict. In MTX treated patients, clearance has been estimated to be 44% lower (ie AUC approximately doubled) than in patients not treated with MTX.

Clinical efficacy

Clinical trials were performed according to GCP requirements a stated by the applicant.

Comparability

Experience with the formulation for marketing was obtained in a comparative single-dose trial in healthy volunteers, which met bioequivalence criteria for C_{max} and AUC in comparison with a clinical trials formulation. AAA responses to the two formulations tested were similar. Additional data on comparative efficacy and clinical safety were obtained in Open Label Extension trials, and did not show obvious differences between the formulation for marketing and the previously used formulation.

Further experience regarding the immunogenicity of the final formulation will be gained from the post-marketing setting.

Dose-response studies and main clinical studies

The efficacy and safety of adalimumab was mainly evaluated in 4 multicentre randomised double blind placebo controlled studies (DE009, DE011, DE019, and DE031) in rheumatoid arthritis patients. The following table summarises some of the characteristics of the clinical studies programme.

Table 1 Overview of clinical study program

Study category	Study	Location	Study characteristics	Dose(s) of adalimumab and route	Duration of study	Number enrolled
Adequate and Well-Controlled Studies	DE009	NA	Multicenter, placebo-controlled, in patients concomitantly treated with MTX	20, 40, or 80 mg every other week, subcutaneous	24 weeks	271
	DE011	EU, AUS, CAN	Multicenter, placebo-controlled, with no concomitant DMARDs	20 or 40 mg, weekly or every other week, subcutaneous	26 weeks	544
	DE019	NA	Multicenter, placebo-controlled, with MTX, investigates joint erosion	20 mg weekly or 40 mg every other week, subcutaneous	52 weeks	619
	DE031	NA	Multicenter, placebo-controlled, with DMARDs, NSAIDs, or steroids	40 mg every other week, subcutaneous	24 weeks	636
Clinical Pharmacology Studies	DE001/DE003 (pbo-ctrl)	EU	Multi-center, placebo-controlled, single dose	0.5, 1.0, 3.0, 5.0, or 10.0 mg/kg, intravenous	≥6 weeks	120
	DE004 (pbo-ctrl)	EU	Multicenter, placebo-controlled	0.5 mg/kg weekly, subcutaneous	12 weeks	24
	DE005/DE005X (pbo-ctrl)	NA	Multicenter, placebo-controlled, single dose, with concomitant MTX	0.25, 0.5, 1.0, 3.0, or 5.0 mg/kg, intravenous	≥6 weeks	60
	DE007 (pbo-ctrl)	EU	Multicenter, placebo-controlled	20, 40, or 80 mg weekly, subcutaneous	12 weeks	284
	DE010 (pbo-ctrl)	EU	Multicenter, placebo-controlled, single dose, with concomitant MTX	1.0 mg/kg, intravenous or subcutaneous	≥6 weeks	54
Open-Label Continuation Studies or Phases	DE003	EU	Continuation of DE001/DE003 (pbo-ctrl)	0.5, 1.0, 3.0, 5.0, or 10.0 mg/kg every other week, intravenous	3 years	117
	DE004	EU	Continuation of DE004 (pbo-ctrl)	0.5 or 1.0 mg/kg weekly, subcutaneous	2.5 years	22
	DE005X	NA	Continuation of DE005 in RA patients concomitantly treated with MTX	All patients transition to 40 mg every other week, subcutaneous	26 months	58
	DE007 (2 yr)[a]	EU	Open-label continuation of DE007 (1 yr), with 3 dose levels in RA patients	20, 40, or 80 mg weekly, subcutaneous	2 years	271
	DE009X	NA	Continuation of DE009, in patients concomitantly treated with MTX	40 mg every other week, subcutaneous	8 months	250
	DE010	EU	Continuation of DE010 (pbo-ctrl), in RA patients with concomitant MTX	1.0 mg/kg every other week, subcutaneous	2.5 years	53
	DE018	EU, AUS, CAN	Continuation for European studies DE003, DE004, DE007, DE010, DE011	40 mg every other or 40 mg weekly, subcutaneous	96 weeks	794
	DE020	NA	Continuation for North American studies DE005X, DE009X, and DE031	40 mg every other week, subcutaneous	Open-ended	810

AUS: Australia; EU: Europe; NA: North America (including U.S. and Canada); CAN: Canada. MTX = methotrexate

[a] Includes a 9-month blinded continuation period that followed DE007 (pbo-ctrl) prior to the start of the open-label phase.

Dose response studies

The results of supportive Study DE007 were used to determine the doses for the pivotal studies DE009, DE011, DE019 and DE031. In study DE007, no difference in efficacy was observed between patient groups receiving adalimumab at 20 mg weekly, 40 mg weekly and 80 mg weekly at the 12-week endpoint. Based on this finding, 40 mg every other week (eow) (equivalent to 20 mg weekly) was selected as the middle dose for Study DE009 and the key dose for studies DE019 and DE031.

Study DE011 continued to explore the dose-response relationship in patients not taking concomitant MTX, and is supported by Study DE007. Study DE001/003 further supported the definition of the dose-response curve for patients not taking concomitant MTX by providing information about the plateau of the dose-response curve.

Among the trials, study DE009 defined the dose-response relationship in patients taking concomitant MTX. Therefore, studies DE019 and DE031 did not investigate different dose intensities. The overall outcome data from the pivotal trials are presented in Table 3.

Overall, it appears reasonably documented that the proposed dose of 40 mg eow provides levels of adalimumab related to a near-maximal response in the majority of patients.

Main studies (phase III)

1. Description of the studies

The efficacy of adalimumab in the targeted indication has been demonstrated in four clinical trials (DE009, DE011, DE019, DE031) in adult patients with, on average, long-standing, moderately to severely active RA, and with experience of previous DMARD therapy (adalimumab n=1,368, placebo n=685). Patients with significant renal or hepatic disease, underlying cardiac or pulmonary disease of significance, history of tuberculosis, immune deficiency, history of malignancy, were not included in the studies.

The following general characteristics applied to the trials:

- All trials had at least 24 weeks of double blind treatment phase (DE019 52 weeks). DE 031 was primarily a safety study. ACR20 responder rate was the primary signs and symptoms endpoint. The primary focus of DE019 was a 52-week X-ray analysis.
- All trials were placebo-controlled. There was no comparison with other DMARD.
- DE009, DE 011 and DE019 enrolled **only** patients who had failed at least one DMARD, DE031 could enroll DMARD-naive patients. Eventually, very few such patients (adalimumab n=21, placebo n=21) were recruited. Prior DMARD experience included MTX in almost all patients.
- Adalimumab was tested as add-on to MTX (10-25 mg wk, median 15 mg, folate in approximately 50%) in DE009 and DE019, as monotherapy after washout of all prior DMARD in DE011, and concomitantly with any DMARD except Azathioprine, Cyclosporin A or other anti-TNF, or as monotherapy in DE 031.
- All trials used SC administration of adalimumab. Doses evaluated varied between 20 and 80 mg, given every other week or weekly (20-40 mg).

The difference to placebo in ACR20 responder rate (a 20% improvement in the ACR response criteria) at 24-26 weeks was the primary efficacy endpoint trials DE09, DE011, and DE019 and the secondary end point in trial DE031. Although at some variance with the CPMP Points to Consider (PtC) guidance document, ACR20 has been generally accepted as primary efficacy measure in recent DMARD procedures.

ACR50, ACR70, HAQ, SJC, TJC, C-reactive protein, and a number of visual analogue scores were evaluated as secondary endpoints. A number of other measures, relevant to the medical impact of adalimumab on RA were also included. Health related quality of life was evaluated by secondary endpoints of HAQ, SF-36 and in some studies, FACIT-F, MAF, EuroQOL and HUI.

2. Statistical analysis

The primary analysis set was mITT (all randomised patients who had received at least one dose of study drug) and the basic analysis for ACR 20 was observed data, withdrawals = non-responders. LOCF was supplementary. This is considered appropriately conservative. In all trials except DE031, ACR response was assessed by especially trained joint assessors, blinded to treatment group.

Continuous efficacy variables were analysed by ANCOVA, using LOCF imputation for missing data.

In addition to the above, a large number of exploratory subgroup analyses were performed, relating to demographic and baseline characteristics.

RESULTS

Study populations/accountability of patients

All confirmatory trials included adult patients only, and patients with chronic juvenile arthritis were excluded. Typically, the study population was characterised by seropositive RA of long duration and with moderate (to severe) ongoing activity.

Efficacy results

Symptoms and signs variables

ACR

The ACR 20 response to adalimumab was superior to placebo in all trials and at all tested doses.

The outcomes for the secondary endpoints ACR50 and ACR70 were consistent with the primary analysis. ACR outcome data from the primary efficacy trials and for the dose proposed by the Applicant (40 mg eow) are shown in Table 2 below.

Table 2: ACR Responses in Pivotal Trials (Percent of Patients)

Response	Study DE009[a]*		Study DE011[a]*		Study DE019[a]*	
	Placebo/ MTX[c] n=60	Humira[b]/ MTX[c] n=63	Placebo n=110	Humira[b] n=113	Placebo/ MTX[c] n=200	Humira[b]/ MTX[c] n=207
ACR 20						
6 months	13.3 %	65.1 %	19.1 %	46.0 %	29.5 %	63.3 %
12 months	NA	NA	NA	NA	24.0 %	58.9 %
ACR 50						
6 months	6.7 %	52.4 %	8.2%	22.1 %	9.5 %	39.1 %
12 months	NA	NA	NA	NA	9.5 %	41.5 %
ACR 70						
6 months	3.3 %	23.8 %	1.8 %	12.4 %	2.5 %	20.8 %
12 months	NA	NA	NA	NA	4.5 %	23.2 %

[a] Study I at 24 weeks, Study II at 26 weeks , and Study III at 24 and 52 weeks

[b] 40 mg Humira administered every other week

[c] MTX = methotrexate

*p<0.01, Humira versus placebo

As noted with other anti-TNF therapies, the onset of response was quick: ACR20 response rates at week 1 (DE009) or week 2 (DE011, DE019, and DE031) were significantly greater than placebo for all adalimumab doses tested. The data for Humira suggest that 'responsiveness' could be determined after 12 weeks of treatment since the number of responders increases very little after this time point. Non-response was noted in at least 30% of the patients. This information has been included in the SPC and is in line with recommendations in recently published consensus documents.

ACR20 parameters

In all four of the confirmatory studies, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. SJC and TJC were reduced by 40-60% compared with baseline, significantly more so than with placebo in all studies and dose groups.

Patient's assessments of pain and disease activity (VAS) were significantly improved *vs.* placebo at all adalimumab doses, except for the 20 mg eow in DE011. A similar pattern was seen for physician's assessment of disease activity.

Mean CRP was significantly reduced *vs.* placebo with adalimumab at the recommended or higher doses in all trials.

Disability

Disability by HAQ (co-primary analysis in DE019 and secondary analysis in the other trials) is summarised in Table 4. A difference of at least 0.22 units is considered clinically relevant. Patients on all adalimumab doses in DE009, DE011, DE019, DE031 had a significant mean HAQ response of at least 0.22 units that was not reached with placebo. A stricter response criterion of 0.50 units (for which there is also published support) was reached with the recommended dose of adalimumab in all studies except monotherapy trial DE011.

Morning stiffness was evaluated at 24-26 weeks in DE011, DE019, DE031. Duration of morning stiffness was significantly reduced with dose intensities of adalimumab ≥20 mg wk/40 mg eow.

X-ray analyses

The findings for the Total Sharp X-ray Score (TSS) from DE019 given in Table 5 show that adalimumab had a significant effect. Joint Space Narrowing (JSN) and erosion scores also showed significant effects of adalimumab.

The effects on X-ray findings were (numerically) consistent for a large number of subgroups tested. There was no difference between ACR20 responders and nonresponders (placebo or adalimumab) regarding mean or median TSS change over one year.

Markers of cartilage destruction (proMMP-1, proMMP-3) were analysed in DE019 and DE009. These were indicative of effects of adalimumab.

It is acknowledged that 52-week data from the ongoing two-year trial DE019 showed statistically significant effects of adalimumab 40 mg eow as add-on to MTX vs. MTX alone on validated measures of structural joint damage. However at least two-year data has been requested for a therapeutic indication of this kind.

Table 3 ACR20 response: number (%) of patients responding by randomised treatment group in the adequate and well-controlled studies

		Adalimumab											
	Concomitant	20 mg eow		20 mg wk		40 mg eow		40 mg wk		80 mg eow		Placebo	
Time point	DMARDs	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Study DE009	MTX												
Week 24		67	32 (47.8)***	NA	NA	63	41 (65.1)***	NA	NA	70	46 (65.7)***	60	8 (13.3)
Study DE011	None												
Week 26		106	38 (35.8)**	112	44 (39.3)***	113	52 (46.0)***	103	55 (53.4)***	NA	NA	110	21 (19.1)
Study DE019	MTX												
Week 24		NA	NA	212	129 (60.8)***	207	131 (63.3)***	NA	NA	NA	NA	200	59 (29.5)
Week 52		NA	NA	212	116 (54.7)***	207	122 (58.9)***	NA	NA	NA	NA	200	48 (24.0)
Study DE031	Any[a]												
Week 24		NA	NA	NA	NA	315	167 (53.0)***	NA	NA	NA	NA	315	110 (34.9)

Comparison *versus* placebo (Pearson's chi-square test): *p≤0.05, **p≤0.01, ***p≤0.001 MTX = methotrexate

[a] Except azathioprine, cyclosporine, and anti-TNF antibodies

Table 4 Disability index of the HAQ by randomised treatment group in the adequate and well-controlled studies

	Adalimumab										Placebo	
	20 mg eow		20 mg wk		40 mg eow		40 mg wk		80 mg eow			
Time point	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Study DE009												
Baseline	67	1.49 ± 0.61	NA	NA	63	1.54 ± 0.61	NA	NA	70	1.51 ± 0.64	60	1.61 ± 0.62
LOCF Change at Week 24	67	-0.54 ± 0.59***	NA	NA	63	-0.58 ± 0.59***	NA	NA	70	-0.59 ± 0.53***	60	-0.23 ± 0.53
Study DE011												
Baseline	106	1.88 ± 0.60	112	1.88 ± 0.63	112	1.83 ± 0.59	102	1.83 ± 0.57	NA	NA	109	1.88 ± 0.64
LOCF Change at Week 26	106	-0.29 ± 0.63**	112	-0.39 ± 0.62***	112	-0.38 ± 0.60***	102	-0.49 ± 0.54***	NA	NA	109	-0.07 ± 0.49
Study DE019												
Baseline	NA	NA	212	1.44 ± 0.64	204	1.45 ± 0.63	NA	NA	NA	NA	198	1.48 ± 0.60
LOCF Change at Week 24	NA	NA	212	-0.60 ± 0.52***	204	-0.56 ± 0.52***	NA	NA	NA	NA	198	-0.24 ± 0.52
LOCF Change at Week 52	NA	NA	212	-0.62 ± 0.55***	204	-0.59 ± 0.58***	NA	NA	NA	NA	198	-0.25 ± 0.56
Study DE031												
Baseline	NA	NA	NA	NA	312	1.37 ± 0.62	NA	NA	NA	NA	314	1.43 ± 0.60
LOCF Change at Week 24	NA	NA	NA	NA	312	-0.51 ± 0.56***	NA	NA	NA	NA	314	-0.26 ± 0.48

Comparison *versus* placebo: ANCOVA (treatment group and baseline): *p≤0.05, **p≤0.01, ***p≤0.001

Table 5 Modified total Sharp x-ray score changes (extrapolated) at Weeks 24 and 52 by randomized treatment group (full analysis set)

	Adalimumab								Placebo			
	20 mg weekly				40 mg eow							
Time point	N	Mean ± SD	Median	Range	N	Mean ± SD	Median	Range	N	Mean ± SD	Median	Range
Baseline	201	66.4 ± 56.3	48.5	(2.0-280.0)	194	72.1 ± 60.7	54.5	(1.5-308.5)	184	66.4 ± 47.4	55.5	(0.5-230.5)
Change at Week 24	196	0.6 ± 4.9**	0.0	(-27.5-50.5)	183	0.3 ± 4.5***	0.0	(-18.0-46.0)	172	1.3 ± 3.7	0.5	(-22.5-15.0)
Change at Week 52	196	0.8 ± 4.9***	0.0	(-14.5-50.5)	183	0.1 ± 4.8***	0.0	(-37.0-23.5)	172	2.7 ± 6.8	1.0	(-25.0-39.0)

Note: an overall comparison of the treatment groups demonstrated a statistically significant difference (p≤0.001)
Statistically significantly different from placebo based on median values: **p≤0.01, ***p≤0.001

Health-related Quality of Life

A number of HRQoL measures (apart from HAQ) were analysed as secondary variables.

Potentially clinically important mean changes (≥5 points) from baseline to Week 24 (Studies DE009, DE019, and DE031) and Week 26 (Study DE011) in LOCF SF-36 PCS scores were shown in the adalimumab 20 mg wk and 40 mg eow across all 4 studies. These changes in SF-36 were associated with decreases (-0.38 to -0.58) in the disability index of the HAQ.

LOCF mean changes from baseline FACIT scores exhibited associations with LOCF mean changes from baseline SF-36 vitality domain scores. The adalimumab 40 mg eow group in the three studies that measured FACIT (Studies DE009, DE019, and DE031) showed improvements of 6.9 to 8.1 from baseline, which corresponded to LOCF mean increases from baseline in the SF-36 vitality domain scores of 16.0 to 18.3. Changes in MAF scores from Study DE031 support this finding. Both increasing FACIT scores and decreasing MAF scores indicate a reduction of fatigue.

Immunogenicity and impact on efficacy

Human antibodies against adalimumab (AAA) were detected and quantified with the help of reference anti-adalimumab antibodies from immunised rabbits. The criteria for robust characterisation of AAA-positivity were well discussedin the dossier, and cut-off criteria used seem justified. These criteria were associated with a false positive rate of approximately 5%.

In the pivotal trials, AAA were identified in 58/1,053 (5.5%) patients treated with adalimumab, compared with 2/370 (0.5%) on placebo. In patients not given concomitant MTX, the incidence was 12.4%, compared with 0.6% when adalimumab was used as add-on to MTX. There was a trend to less AAA development with higher doses and more frequent administration of adalimumab, noticeable especially when MTX was not used. Apart from MTX +/-, there were no specific demographic or baseline variables associated with risk for AAA response. Few AAA +ve patients withdrew due to lack of efficacy, but, on average, AAA-positivity was associated with a reduced response to adalimumab.

The Applicant suggests that efficacy failure due to AAA on adalimumab 40 mg eow (in patients not on concomitant MTX) might be overcome by increasing the dose to 40 mg wk. The support for this comes from trial DE007, where 4/4 AAA +ve ACR20 non-responders on 20 mg wk responded when the dose was increased to 40 mg wk. Moreover, data from open label long term extension studies further support this approach.

In summary, coadministration of adalimumab with MTX reduces the clearance of adalimumab and the likelihood of AAA formation. The neutralising effects of AAA may be reversed with increasing the dose intensity to 40 mg weekly For best efficacy adalimumab should be used together with MTX and monotherapy should be reserved for situations of intolerance to MTX or when treatment with MTX is inappropriate.

Exploratory analysis performed across trials.

ACR20 responses at 24-26 weeks (pooled data) were further analysed for a number of subgroup interactions and the following findings were observed:

There was a trend to decreasing response to adalimumab 40 mg every other week (eow) with increasing body weight (59.7% for patients ≤60 kg, compared with 46.5% for patients 85-100 kg). Whether the trend observed is clinically relevant or not is debatable.

There were no differences in response to adalimumab over the range of RA duration studied, with regard to RF status (+/-) at baseline, or with regard to disease activity at baseline (TJC, SJC, HAQ, CRP). There was, however, a trend to decreasing response with increasing experience of previous DMARD therapy (62% for patients exposed to 1 previous DMARD, 49% for patients having taken >4

previous DMARDs). Drug-disease interactions were studied for the presence or absence of diabetes mellitus, CHF, COPD, hypertension, asthma and renal impairment. Significant interaction (Breslow-Day) with decreased response with presence of concomitant disease was seen for hypertension and asthma. The asthma group however was small. The clinical relevance of the statistically significant interaction in the group of patients with concomitant hypertension is debatable.

Drug-drug interactions for concomitant antirheumatic therapy are summarised in Table 6.

Table 6 Drug-drug interactions: number (%) of patients with an ACR20 response at Week 24 by concomitant rheumatoid arthritis drug therapies in the adequate and well-controlled studies (observed values)

	Adalimumab				Placebo	
	40 mg eow		All doses			
	N	n (%)	N	n (%)	N	n (%)
Methotrexate						
With	448	273 (60.9)	796	480 (60.3)	459	137 (29.8)
Without	250	115 (46.0)	572	248 (43.4)	226	62 (27.4)
Corticosteroids[a]						
With	352	187 (53.1)	747	390 (52.2)	354	112 (31.6)
Without	346	201 (58.1)	621	338 (54.4)	331	87 (26.3)
NSAIDs[a]						
With	543	302 (55.6)	1062	570 (53.7)	544	163 (30.0)
Without	155	86 (55.5)	306	158 (51.6)	141	36 (25.5)

[a] At baseline

Concomitant use of adalimumab and DMARDs other than MTX was assessed only in DE031 (which was not primarily an efficacy study). This is summarised in Table 7, experience of such use is limited. The apparently poor outcome with adalimumab plus leflunomide is probably explained by the high rate of withdrawals in this group.

Table 7 Drug-drug interactions: number (%) of patients with an ACR20 response at Week 24 by concomitant DMARDs in Study DE031 (observed values)

	ACR20			
	Adalimumab		Placebo	
Concomitant medication	N	% Response	N	% Response
Methotrexate[a]	178	56.7	199	35.2
Antimalarial[a]	75	50.7	82	32.9
Leflunomide[a]	42	33.3	46	37.0
Sulfasalazine[a]	29	58.6	33	24.2
Other DMARDs[a]	25	52.0	25	44.0
No DMARD	54	50.0	45	33.3
One DMARD	184	55.4	172	37.8
Two DMARDs	66	50.0	84	29.8
Three or more DMARDs	11	45.5	14	35.7

Antimalarial (e.g., hydroxychloroquine, chloroquine) MTX = methotrexate
Other DMARDs (e.g., gold preparations, penicillamine, and other drugs)
[a] Patients could be represented in more than 1 category

Supportive studies

Clinical Pharmacology Trials:
Trials DE001, DE004, DE005, DE007, DE010 provided some supportive efficacy data for various dose regimens of adalimumab. In these trials, altogether 401 patients were exposed to adalimumab. Of principal interest are the 12-week placebo-controlled DE004, DE007, which explored SC doses of 20-80 mg wk. Generally, the ACR20 responses mirrored those described in pivotal trials.
Long-term trials:
A number of long-term, open-label trials (DE003, DE004, DE005X, DE007, DE009X, DE010, DE018, and DE020) are described, including trials rolling over patients from the six-month pivotal trials. These include 1,785 patients. ACR20 is available for up to 36 months (n =134). Data are consistent regarding maintenance of efficacy on symptoms and signs.

Discussion on clinical efficacy

Efficacy on symptoms and signs

The ACR20 response to adalimumab was superior to placebo in all trials and at all tested doses. The outcomes for the secondary endpoints ACR50 and ACR70 were consistent with the primary analysis.

Additional support for clinically relevant efficacy was gained from outcomes for ACR component parameters, disability by HAQ, morning stiffness, and from an array of HRQoL variables. As with other TNF antagonists, onset of relief of symptoms and signs was rapid, and was maintained for the duration of controlled and Open Label Extension (OLE) clinical trials presented. Even at the highest dose tested and with concomitant MTX, non-response was noted in at least 30% of patients. Similar findings have been made with other TNF antagonists. The Applicant has provided further analyses indicating that the clinical response is usually achieved within 12 weeks. This has been reflected in the SPC.

Based on across-studies comparisons, efficacy of adalimumab was better with concomitant use of MTX (DE009, DE019) than as monotherapy (DE011). This may be explained partly by additive anti-inflammatory effects of adalimumab and MTX, but appears more likely due to increased exposure to adalimumab in the presence of MTX, secondary to reduced AAA-mediated clearance of adalimumab. AAA are neutralising on efficacy of adalimumab and appear at much greater incidence when given as monotherapy. Additional analyses indicate that in AAA +ve patients, the median long-term signs and symptoms response to adalimumab in monotherapy is near zero. Based on these considerations, adalimumab should be used primarily in combination with MTX.

Monotherapy should be reserved for patients intolerant to MTX and for situations when continued therapy with MTX is considered otherwise inappropriate. In monotherapy, available data from Phase II and OLE studies indicate potential benefit of increased dose intensity in patients exhibiting loss of response to adalimumab at the recommended dose. Appropriate information has been included in the SPC.

Efficacy on joint destruction

Trial DE019 provided 12-month data on X-ray analysis (modified Sharp scores) of progression of joint destruction. Significant and relevant preventive effects were seen with adalimumab in combination with MTX *vs.* MTX alone, and were of similar magnitude as have been observed with other agents of this class. While it is acknowledged that the 52-week data from the ongoing two-year trial DE019 showed significant effects of adalimumab 40 mg eow as add-on to MTX vs. MTX alone on validated measures of structural joint damage, at least two-year data has been requested for a therapeutic indication of this kind.

Clinical safety

Patient exposure

Overall summaries of the number of subjects exposed are given in the following Table. The size of the data-base is considered acceptable for a product of this kind.

Table 8
Subjects exposed to study drugs in adalimumab studies

Study category	Number of unique subjects exposed to adalimumab	Number of unique subjects exposed to placebo
Clinical pharmacology (volunteers)	241	20
Clinical pharmacology (RA patients)	402	140
Adequate and well-controlled	1380	690
Open-label continuation studies	552[a]	0
Total	2575	850

[a] Subjects who received adalimumab for the first time during an open-label continuation study.

Adverse events (AE) and serious adverse events (SAE)

Generally, the safety profile of adalimumab appears comparable with that of other TNF-antagonists

Significantly higher incidences of abdominal pain, hypertension and headache were noted with adalimumab compared with placebo. The reason for this increased incidence is not definitely known. This phenomenon has been seen with other therapeutic agents recently approved for the treatment of RA and the incidence of abdominal pain and headache reported during the clinical trials with adalimumab is consistent with these other agents.

- *Infections*

In placebo-controlled trials, the rate of infection was 1 per patient year in the Humira treated patients and 0.9 per patient year in the placebo-treated patients. The incidence of serious infections was 0.04 per patient year in Humira treated patients and 0.02 per patient year in placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on Humira after the infection resolved.

In addition, sepsis, tuberculosis and other opportunistic infections were reported in clinical trials with adalimumab. Thus, the signal that anti-TNF therapy for RA may be associated with serious infection is confirmed for adalimumab. There were some deaths due to infections (see section on 'Deaths').

Overall, adalimumab appears to have class-typical effects on the risk for reactivation of tuberculosis. This has been reflected in SPC and PL. A patient alert card (that is a part of the labelling information) has been introduced to address the risk of tuberculosis.

- *Malignancies*

There is some remaining concern that anti-TNF therapy may increase the long-term risk of malignancy in RA patients. In the adalimumab development programme, 53 malignancies were diagnosed in 52 patients treated with adalimumab. This included 4 cases of non-Hodgkins lymphoma (NHL) of variable histological types. There were no cancers, excluding two non-melanoma skin cancers in the placebo group (which contributed some 13% of the total observational experience). There was no trend to increased event rate with time on adalimumab and, overall, the incidence rate was not significantly different from that expected from NCI SEER data.

- *Immunologic reactions*

Hypersensitivity reactions

Thirty-eight patients (1.6% of 2,334 patients) experienced AEs characterised as immunologic reactions, which included events that were classified as either AEs or SAEs. Four patients receiving SC adalimumab had systemic reactions that were characterised as 'anaphylactoid-type' reactions. These included rash, tachycardia, dizziness, fatigue, oedema, and dyspnoea. At least one of these patients had multiple episodes. None of these reactions were serious and all were treated in the

outpatient setting. Fourteen patients developed rash that was considered by the investigators to be allergic in nature. Six patients had urticaria-type rashes without other etiology. Two patients had fixed drug eruption rash, one had a cutaneous rash on the abdomen with histology showing deposition of immunoglobulin and complement. Three other patients had non-specific allergic reactions that could not be definitively related to another etiology with the information that was collected. No patient receiving SC adalimumab required hospitalisation for an anaphylactic-type reaction.

Injection site reactions (ISR)

In placebo-controlled trials, 20% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 14% of patients receiving placebo. There was no relationship between the occurrence of injection site reactions and the presence of AAA. There was a trend towards decreased rates of injection site reactions in patients taking concomitant MTX. Injection site reactions tended to be either mild or moderate and rarely led to discontinuation of therapy.

Anti-DNA antibodies (ANA) and lupus

Four adalimumab-treated patients developed illness that was designated by the investigators as lupus-like in character, and related to study drug.
In the pivotal trials, ANA titres were determined at baseline (prior to the first dose of adalimumab or placebo) and at one or more time points during the first 12 weeks of study drug, and at the end of 6 months of treatment. After 6 months of treatment with adalimumab, 132 (12.6%) of 1,046 baseline negative patients had titres ≥1:80; by comparison, after 6 months of treatment with placebo, 39 (7.3%) of 532 baseline negative patients had ANA titres ≥1:80.

Safety impact of AAA positivity

As noted above, the rates of AAA formation were different with concomitant MTX (4 of 628 [0.6%]) *vs.* without concomitant MTX (54 of 434 [12.4%]).

The impact of AAA on overall safety is best analysed in DE011, the placebo-controlled, European monotherapy trial, which also contained the great majority of AAA +ve cases. There were no major differences between groups. For specific AEs, it could be noted that rash, pruritus and injection site reaction incidences did not differ between AAA +ve and –ve patients. AAA.

There is no information about the potential of reactivity between anti-infliximab HACA and adalimumab and the implications for patients transferring from infliximab to adalimumab.

Safety impact of dose interruptions

No specific AE profile was noted in the 21 patients restarted on adalimumab after >140 days' interruption.

- *Demyelinating disease*

TNF antagonist therapy has been associated with exacerbation of demyelinating disease. During the adalimumab development program, two RA patients and one volunteer developed demyelinating disease. There are no firm indications that the risk with adalimumab is greater than with other products in the class.

- *Haematologic events*

Events associated with myelosuppression or depressed platelet counts are of special concern for anti-TNF therapies. Four adalimumab-treated patients experienced pancytopenia or agranulocytosis. The data for patients who experienced CTC Grade 3 or 4 abnormalities of WBC, neutrophil numbers (recorded as neutrophil percent or absolute neutrophil count), or platelet count were also evaluated.

There were no reports of CTC Grade 4 leukopenia. Six patients experienced CTC Grade 3 leukopenia, including four patients who also experienced CTC Grade 3 or 4 neutropenia. In addition to these four patients, seven patients had relative or absolute neutropenia. Grade 3 thrombocytopenia was noted in one patient on adalimumab. No follow-up data after cessation are available. A myelosuppressive effect of adalimumab cannot be ruled out.

- *Congestive heart failure (CHF)*

Only isolated patients with a history of CHF were enrolled to adalimumab trials. Based on previous experience with other TNF-antagonists, Humira is contraindicated in moderate to severe heart failure (NYHA class III/IV) and should be used with caution in patients with mild heart failure. The patient alert card that has been included in the labelling information also addresses the risk of CHF.

- *Drug-drug interactions*

Concurrent MTX increases exposure to adalimumab by approximately 40%. Across all study groupings, the percentage of patients reporting SAEs was slightly higher among patients not taking concomitant MTX than among patients taking concomitant MTX. The overall pattern of SAEs was generally unaffected by the presence or absence of MTX as a concomitant medication.

Use of MTX was associated with a decrease in the percentage of immunologic reactions. Twenty-nine (2.4%) of 1186 patients not receiving MTX developed an AE characterised as an immunologic reaction, while only 9 (0.8%) of 1,148 patients receiving concomitant MTX developed an immunologic reaction.

An immune function sub-study to DE019 is presented (adalimumab plus MTX n=46, MTX plus placebo n=18). This included response to pneumococcal vaccine. The results are acceptably summarised in the SPC and do not create additional concerns regarding immunosuppression with the combination.

Serious infectious AEs occurred at a slightly higher percentage in adalimumab-treated patients taking corticosteroids at baseline than those adalimumab-treated patients not taking corticosteroids. This was noted in the adequate and well-controlled studies, the open-label continuation studies, and in all studies of RA patients.

No influence on safety profile was noted for concomitant use of NSAIDs.

Use of adalimumab with DMARDs other than MTX was studied in DE031. As noted above experience is limited. No specific concerns are apparent at this stage.

Deaths

A total of 22 adalimumab-treated patients and 2 placebo-treated patients died as a result of AEs during the development program. In addition, two patients died of cardiovascular disorders 33 and 36 days after their final doses of study drug in Study DE020. Five deaths were deemed related to infections, including three cases of sepsis, on case of aspergillosis, and one case of super-infected herpes zoster. Six deaths were related to malignancies and four deaths were due to cardiovascular disease.

Laboratory findings

The summary of laboratory adverse events is comprehensive and the following findings are adequately reflected in the SPC: increased coagulation time, decreased haemoglobin, hypercholesterolaemia, hyperlipaemia, increased ALT, increased BUN, and haematuria.

Discussion on clinical safety

Qualitatively, the safety profile of adalimumab appears typical for that of anti-TNF therapy. Increased risk of infection, Tuberculosis and other opportunistic infection, demyelinating neurological events, and formation of auto-antibodies were identified in the trial programme. These issues are adequately resolved through SPC amendments and post-marketing surveillance. There were no serious administration reactions and the incidence of ISR was low. There are no indications that AAA affect the safety profile.

AAA are formed in a percentage of patients, especially when adalimumab is used without concomitant MTX. AAA have not been associated with specific adverse events so far. As AAA may impact therapeutic response monotherapy should be used only in patients intolerant of concomitant MTX.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
Viral Safety and Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that adalimumab was effective in *in vitro* and *in vivo* studies. A number of general pharmacology/safety pharmacology studies were performed. There were no findings in these studies that raise concerns.

In mice and monkeys, the pharmacokinetics of adalimumab were linear as long as anti-adalimumab antibodies were absent. However, both MAHA and PAHA developed after single doses, and affected the elimination. Thus, parameters such as clearance and half-life could not be determined with certainty. In general though, elimination was slow in both species ($t_{1/2}$ about 14 –21 days in monkeys).

The toxicology program included studies of single and repeat dose toxicity, genotoxicity, developmental toxicity and local tolerance. An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomologous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Carcinogenicity studies, and standard assessment of fertility and postnatal toxicity, were not performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and the development of neutralizing antibodies in rodents.

Clinical efficacy and safety

The documentation submitted provides clear evidence of efficacy of adalimumab in the population of adult patients with moderate to severe, active RA, who have failed previous DMARD therapy, including MTX. The magnitude of effect on symptoms and signs variables appears typical for anti-TNF therapy and has been documented for sufficient duration in add-on to MTX. Due to higher incidence of AAA formation and on average loss of efficacy, monotherapy should be reserved mainly for patients intolerant to MTX. In the chronic population with relatively low erosive activity studied, there is also a significant effect on joint destruction when adalimumab is used as add-on to MTX, documented up to one year. Full assessment of the relevance of this will have to await the 2-year data, however.

The clinical comparability data available are limited, but show bioequivalence between clinical trial and commercial materials as regards pharmacokinetics, and do not indicate major differences for short-term immunogenicity or overall efficacy and safety. Further reassurance will be provided from a

long-term post-marketing trial. Also further characterisation of kinetics and dynamics of antibody formation to adalimumab will be provided post-authorisation from another trial

The overall safety profile of adalimumab appears typical of anti-TNF therapy. Therefore, in most areas the safety information was harmonised with that for infliximab and etanercept . The incidence of serious hypersensitivity reactions appears reassuringly low, as does the incidence of ISR.

Benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Humira was favourable and therefore recommended the granting of the marketing authorisation, for the indication: "Treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate. To ensure maximum efficacy, Humira is given in combination with methotrexate. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

GLOSSARY

AAA	Anti-adalimumab antibodies
ACR	American College of Rheumatology
ACR100	A 100% improvement on the ACR response criteria
ACR20	A 20% improvement on the ACR response criteria
ACR50	A 50% improvement on the ACR response criteria
ACR70	A 70% improvement on the ACR response criteria
AE	Adverse events
ALT	Alanine transaminase
ANA	Ant-DNA antibodies
ANCOVA	Analysis of covariance
AUC	Area under the curve
BUN	Blood urea nitrogen
CHF	Congestive heart failure
C_{max}	Maximum serum concentration
CL	Clearance
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CTC	Common Toxicity Criteria (National Cancer Institute)
DMARD	Disease-modifying anti-rheumatic drug
eow	Every other week
FACIT	Functional assessment of chronic illness therapy (fatigue scale)
GCP	Good clinical practice
HACA	Human anti-chimeric antibody
HAMA	Human anti-mouse antibody
HAQ	Health assessment questionnaire
HRQOL	Health-related quality of life
HUI	Health utilities index
IL	Interleukin
ITT	Intention to treat
ISR	Injection site reaction
JSN	Joint space narrowing
LOCF	Last observation carried forward
MAF	Multidimensional assessment of fatigue
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PAHA	Primate anti-human antibody
ProMMP	1-Pro-matrixmetalloproteinase-1
ProMMP	3-Pro-matrixmetalloproteinase-3
PL	Package Leaflet
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse reactions
SC	Subcutaneous
SJC	Swollen joint count
TJC	Tender Joint Count
SPC	Summary of product characteristics
TNF	Tumor necrosis factor
TSS	Total sharp X-ray score
VAS	Visual analog scale
WBC	White blood cells
QOL	Quality of life