SCIENTIFIC DISCUSSION

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

1. Introduction

Raptiva is indicated in the treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA. An initial single dose of 0.7 mg/kg body weight is given followed by weekly injections of 1.0 mg/kg body weight, subcutaneously. The duration of therapy is 12 weeks. Therapy may be continued only in patients who responded to treatment (PGA good or better).

Psoriasis vulgaris is a chronic, inflammatory, skin disorder that affects 0.5% up to 3% of world's population. It is a T-cell mediated immune disorder in which CD4+ and CD8+ memory T cells stimulate the hyperproliferation of keratinocytes. The disease is characterised by a fluctuating course of remissions and exacerbations. Although rarely life threatening, psoriasis is frequently disabling and often compromises quality of life.

Mild psoriasis can be treated by e.g. topical corticosteroids, topical vitamin D derivatives and topical vitamin A derivatives (tazarotene). Currently approved therapies for moderate to severe psoriasis include phototherapy, systemic retinoids, cyclosporine and methotrexate. Based on historical data (e.g. Spuls et al. Journal of Dermatology 1997;137:943-49, VMR Heyendael et al. N Engl J Med 2003; 349: 658-65, CEM Griffiths et al. Health Technology Assessment 2000; vol.4: No. 40, VC HO et al. Br J Dermatol 1999; 141: 283-291.), current therapies appear to be very effective, especially UVB, PUVA, methotrexate and cyclosporin; PASI75 is reached in 60 to 90 % of patients with these treatments, retinoids appeared less effective but still PASI75 is reached in around 50%. Treatment strategies with existing therapies are variable but in any case, as soon as clearance or "almost-clearance" is obtained, it is good practice to stop or reduce treatment doses in order to limit long-term toxicity.

The Applicant Serono Europe Limited has submitted an application for a European Marketing Authorisation for its product Raptiva through the Centralised Procedure. This application concerns a complete and independent application concerning a new active substance according to article 8.3 (i).

Efalizumab, the active substance of Raptiva, is a recombinant humanised monoclonal immunoglobulin G1 (IgG1) antibody with immunomodulatory properties.

The to-be-marketed formulation is a subcutaneous (s.c.) formulation (lyophilised powder) produced by Genentech. Most of the non-clinical programme was performed, using an intravenous (i.v.) formulation (solution) of efalizumab produced by XOMA. Both the XOMA material and the Genentech material evoked the primary pharmacological response.

In the clinical programme, most of the phase I- II programme was performed, using the intravenous (i.v.) formulation. In the first pivotal clinical phase III study ACD2058g the Xoma s.c. formulation was used. In phase III study ACD2059g both formulations were used. Phase III studies ACD2390g, ACD2600g and IMP24011 used efalizumab produced by Genentech, administered subcutaneously.

There is no paediatric development programme for efalizumab.

2. Part II: Chemical, pharmaceutical and biological aspects

Introduction

Efalizumab, the active ingredient of Raptiva, is a recombinant humanised monoclonal immunoglobulin G1 (IgG1) antibody with immunomodulatory properties. It binds specifically to the CD11a subunit of LFA-1 (lymphocyte function-associated antigen-1, a leukocyte cell surface protein) and inhibits the binding of LFA-1 to ICAM-1, -2, and -3 (intercellular adhesion molecules 1, 2, and 3) which interferes with lymphocyte adhesion to other cell types. LFA-1 is present on activated T-lymphocytes, and ICAM-1 is up-regulated on endothelial cells and keratinocytes in psoriasis

plaques. By preventing LFA-1/ICAM binding, efalizumab may alleviate signs and symptoms of psoriasis by inhibiting several stages in the immunologic cascade: primary T-lymphocyte activation in lymph nodes, T-lymphocyte trafficking into psoriatic lesions, T-lymphocyte interaction with keratinocytes, secondary activation of T-lymphocytes in plaques, and release of pro-inflammatory cytokines.

Composition

Raptiva is provided as a lyophilised powder for injection in a single use vial, which contains a nominal amount of 125 mg of efalizumab per vial of drug product (total amount 150 mg). Reconstitution of the single-use vial with 1.3 ml of the supplied water for injections (WFI) yields approximately 1.5 ml of solution, of which 1.25 ml is retrievable with a final concentration of 100 mg/mL efalizumab. Raptiva contains as excipients sucrose (lyoprotectant), histidine (buffering agent) and polysorbate 20 (surfactant).

The vial and stopper components comply with Ph. Eur. requirements. The container-closure system consists of 10 cc Type I borosilicate glass vial, 20 mm grey rubber stopper and 20 mm West cap with an aluminum seal and a plastic flip-off cap.

A prefilled diluent syringe delivers 1.3 mL of WFI, and will be included in the final drug product package. The Type I glass syringe and plunger meet Ph. Eur. requirements. The graduation is placed with a label on the syringe.

Drug Substance

Nomenclature

INN Name:	Efalizumab
Compendial Name:	Not applicable
Chemical Name:	Recombinant humanised monoclonal antibody to CD11a
USAN/BAN/JAN Name:	Efalizumab
CAS Registry Number:	214745-43-4
Other Names:	rhuMAb CD11a, anti-CD11a, hu1124 antibody

Description of the Drug Substance
Efalizumab is a full-length IgG1κ isotype antibody composed of two identical light chains (214 amino acid residues) and two identical heavy chains (451 residues). The heavy chain demonstrates C-terminal heterogeneity and also contains one N-linked glycosylation site at asparagine 301. The oligosaccharides are of complex biantennary structures with a core fucose with the two branches terminating mainly with zero, one or two galactose residues. The approximate molecular weight is 150 kD. The heavy and light chains are covalently coupled to each other through inter-chain disulfide bonds consistent with the structure of a human IgG1. Efalizumab is a humanised form of the murine monoclonal antibody MHM24 containing human constant region sequences and murine light and heavy chain Complementarity Determining Region (CDR) sequences. The human IgG1 framework contributes to 90% of the overall protein sequence.

- Manufacturing Process Development

Drug Substance Manufacturing Process Development
Production processes and excipients were optimised over the course of the Efalizumab development. In addition, at the Phase-III stage of clinical trials the manufacturing of Raptiva was moved from the manufacturing site XOMA to Genentech. At the time point of the submission of the application for marketing authorisation, five campaigns of Efalizumab had been produced. In brief, changes in the process included:

- Minor changes to the process due to differences in the facilities, and in order to harmonise the efalizumab process with other processes at Genentech.

- Changes to the cell culture process including scale-up.
- Changes to the purification process including scale-up.
- Changes to the formulation so as to optimise the lyophilisation process.

Drug Substance Formulation Development

The Phase I and II clinical trial (XOMA Q3 96) formulation was developed to target intravenous administration of efalizumab. The drug substance formulation was changed in the XOMA Q2 99 process to allow development of a lyophilised formulation for subcutaneous administration. The drug substance formulation was further optimised in the GNE Q1 00 process. The change in lyoprotectant to sucrose has been demonstrated not to affect the quality. Further changes to improve the buffering capacity were made. This formulation was tested in Phases II and III clinical trials. The Efalizumab Drug Substance formulation has since remained the same.

The comparability of the drug substance manufactured in the various campaigns is discussed in section *Characterisation and Comparabiliy*.

- Manufacture

Genentech, South San Francisco, CA, USA manufactures the drug substance at commercial scale for the market.

The Drug Substance, efalizumab, is a recombinant monoclonal antibody produced in transfected Chinese Hamster Ovarian cells (CHO). It is manufactured by cell culture followed by a purification process. The fermentation is performed in appropriate medium supplemented with other required growth factors, trace elements and other nutrients and reagents.

DEVELOPMENT GENETICS

Efalizumab is expressed by Chinese hamster ovary (CHO) cells, CHO DP-12 cells, a proprietary Genentech cell line derived from CHO-DUX B11. The origin of this cell line is traced back to its origin in 1958. Efalizumab is derived from the murine monoclonal antibody MHM24. The generation of this murine antibody and its subsequent humanisation has been described in the application and in the open scientific literature. The construction of the expression plasmid pSVSDMHM-H.SV-L has been sufficiently described and an annotated sequence map has been submitted .

CHO DP-12 cells were transfected with the expression plasmid. After selection and amplification, an expansion Prebank was established and used to prepare the master cell bank (MCB).

Cell Bank System, Characterisation and Testing

For the production of efalizumab, a two-tiered cell bank system of master cell bank (MCB) and working cell bank (WCB) has been established.

The preparation of the MCB and WCB have been described. Briefly, the preliminary bank was used to prepare the MCB and the MCB was used to prepare the subsequent WCB's. Cells were cultured and expanded in appropriate flasks in growth medium. The resulting cell suspension was harvested, resuspended in medium and distributed in ampoules. The ampoules were frozen. The cell banks are expected to retain viability for an indefinite period.

MCB and WCBs have been tested for the presence of contaminants. Characterization studies were performed to assess adventitious and endogenous agents and to confirm the CHO cell origin of the cell banks. Infectious retrovirus particles were not present. These results are in line with results previously reported for other retrovirus-like particles from the parental CHO-K1 cell line.

New WCB will be produced in line with the protocol that was submitted as part of ther evaluation process.

Genetic Stability
Genetic stability has been assessed by copy number analysis, restriction endonuclease mapping, and nucleotide sequence analysis. The MCB and end of production (EOP) cells were analysed. The copy number does not change between MCB and EOP, the restriction pattern is identical, and the nucleotide sequence is identical within experimental error.
Batch and Scale Definition
The applicant has detailed both the definition of a batch and the actual manufacturing scale used.

Fermentation and Purification
Introduction
The fermentation and purification process have been sufficiently described. The manufacturing process has been defined within the limits supported by process validation and incorporates the experience gained during development and full-scale manufacturing. Furthermore, the application clearly indicates the pre-specified target parameters used to define and operate the manufacturing process. The information in its entirety supports both the robustness of the purification process and demonstrates the consistent manufacture of a highly purified product.

Fermentation
The Efalizumab cell culture process involves three stages: seed train, inoculum train, and the actual production culture using CHO cells in suspension.

The fermentation process has been defined and described. Briefly, the seed train is a continuous long term, culture of cells. The seed train is grown in medium. The inoculum train is used to expand cells from the seed train to a full-scale production culture. It consists of cultures of increasing size. The culture is grown in medium. One batch of harvested cell culture fluid (HCCF) is obtained per culture. Data from the batches submitted sufficiently justify that a target harvest of the production culture at a defined time of culture assures a consistent product.

Purification
The drug substance purification process consists of a number of defined steps leading to manufacture of the Drug Substance.
The purification process has been adequately described. The purification steps include chromatography, viral and ultra/diafiltration and are designed to run continuously and step duration times have been given based on the current manufacturing experience. After these steps, the drug substance (formulated bulk) is formulated by the addition of polysorbate 20 and sucrose.

The sanitisation/regeneration procedures of the chromatography columns have been clearly described and it was sufficiently assured that no virus carry-over occurs with the re-use of the resin/columns. The lifetime of chromatography columns was set based on results from reuse studies. Consistency of chromatography runs is assured by step yield action limits based on currently available data.
Acceptable criteria have been set for the performance of the UF/DF membrane. The prevention of carry-over of viruses is sufficiently assured by the described and validated sanitisation .

- Control of Critical Steps and Intermediates

The manufacturing process of the drug substance is monitored by appropriate in-process controls.

The drug substance manufacturing process is designed to operate continuously without in-process hold steps. On occasion it may be necessary to store an intemediat before proceeding to the next step. The applicant has performed hoding time studies, in which the stability of all intermediates stored during production has been studied and is satisfactorily described.

- Process Validation

Consistency of the cell culture process was validated and shown using full-scale runs. The process was evaluated for robustness and reproducibility. It was demonstrated that the cell culture process

consistently yields material suitable for purification. Consistency of the purification process was validated and shown using several consecutive full-scale runs conducted at the Genentech South San Francisco facility. The process was evaluated for robustness and reproducibility with respect to the removal of cell substrate impurities, process-related impurities and product-related impurities, viral clearance and step yields. It was demonstrated that the purification process yields consistent intermediates and a consistent product. Consistency of product yield for each step and the process as a whole was demonstrated.

- Characterisation and Comparability

The applicant performed an extensive characterisation study to elucidate the structure and other characteristics of Efalizumab. The reference material has been subjected to a throughout characterisation. To evaluate the comparability of the active substance, samples representing the different campaigns have also been characterised. The samples that were analysed included the qualification batches. All batches, except one were used in Phase III clinical trials.

Physiochemical Characterisation

The physiochemical characterisation studies have been performed employing state of the art methods. (Edman degradation; endoproteinase Lys-C peptide map analysis in combination with MS analysis; ESI-MS analysis; Ellman analysis (using DTNB); CE-SDS analysis; Peptide N-Glycosidase F digest in combination with MALDI-TOF/MS; boronate chromatography; cIEF; SEC; HP-IEC). General information on the methods used has been given.

The results for the reference material and the batches analysed were provided in the application. Confirmation that the protein structure was consistent throughout the batches tested and as expected from the primary sequence was obtained.

- The expected masses were confirmed.
- The expected N-terminal sequences of the light and heavy chain were also confirmed.
- Besides the charge heterogeneity caused by enzymatic C-terminal processing, additional charge variants, mainly from chemical modifications, were found. The variants are fully active as determined by the cell adherence inhibition assay.
- Seven glycation sites were identified.
- Confirmation of the expected glycosylation for an antibody produced in CHO cells was found.

Biological Characterisation

Efalizumab blocks the binding of the CD11a subunit of the lymphocyte-associated antigen-1 (LFA-1). The epitope recognized by the murine parent antibody of Efalizumab was mapped.

As shown in the biological characterisation studies, by blocking LFA-1 from binding to ICAM-1 Efalizumab is able to elicit the following in vitro biological responses:

- Inhibition of the mixed lymphocyte response
- Inhibition of T-cell activation
- Down-modulation of CD11a on T-cells
- Inhibition of T-lymphocyte adhesion to human endothelia cells
- Inhibition of transendothelia T-cell migration

Efalizumab binds poorly to complement protein C1q and does not display complement-dependent cytotoxicity (CDC). Efalizumab is recognised by the Fcγ receptor series (FcγRI, FcγRIIA, FcγRIIB and FcγRIIIA). Antibody-dependent cellular cytotoxicity (ADCC) activity is minimal and depends on the level of CD11a expression on the target cell.

Comparability of XOMA and Genentech Material

The results from the biological characterisation studies demonstrated comparable *in vitro* biological activity of XOMA and Genentech material.

Physiochemical characterisation studies revealed differences in glycosylation, C-terminal and charge heterogenity of the drug substance produced at XOMA and Genentech.Based on these results the CHMP concluded, that the Xoma and Genentech batches were not physicochemically comparable.

Consequently, clinical efficacy and safety data with Genetech material were considered pivotal and data with XOMA material were only considered supportive.

- Drug Substance Specification

Appropriate specifications for the drug substance have been set and justified.
The test methods have been sufficiently described and validated according to ICH guidelines. Appropriate reference material has been qualified. The stability of the reference material will be monitored. The tests developed include identity tests, purity tests and assays, including a biological assay for potency testing purposes. The bioassay was sufficiently validated.

Batch Analysis Data
Batch analysis data were provided. The results from the qualification batches were within the drug substance specifications.

- Container Closure System

The drug substance is stored in tanks for long term storage. The containers-closure system of these tanks has been sufficiently described.

- Drug Substance Stability

The applicant provided sufficient stability data during the evaluation process to support the proposed shelf-life for the drug substance.

Drug Product

- Pharmaceutical Development

DRUG PRODUCT DEVELOPMENT
The liquid and the lyophilised formulation development have been thoroughly described and the rationale for the selection of the excipients (sucrose, histidine, polysorbate 20) has been adequately addressed and justified. No novel excipients and no excipients of animal or human origin are used.

Minor changes have been made in the manufacturing process of the drug product. These have been adequately addressed and analytical data confirm comparability. Primary container components are standard for the product type and acceptable.

COMPARABILITY OF CLINICAL TRIAL BATCHES WITH TO-BE-MARKETED BATCHES
The development of the drug substance manufacturing process and the comparability of the clinical trial material produced at XOMA and Genentech with batches intended for marketing were discussed. In summary, given the changes introduced, the CHMP concluded, that the assessment of the clinical efficacy and safety of Raptiva should be based on clinical trials performed with batches produced at Genentech, the to-be-marketed product.

- Manufacture of Drug Product

MANUFACTURING
Details on the manufacturers have been provided. All manufacturing operations for the drug product are performed by Genentech, South San Francisco, CA, USA. Manufacturing operations for the solvent in the prefilled syringes (sterile WFI) are performed at Baxter Pharmaceutical Solutions LLC, Bloomington, IN, USA. Packaging and labelling of the drug product and pre-filled syringe are performed at Industria Farmaceutica Serono SpA, Bari, IT or Laboratories Serono S.A., in Aubonne and Coinsins, CH. The manufacturer responsible for batch release is Industria Farmaceutica Serono SpA, Guidonia Montecelio, IT.
The batch formula for minimal and maximal batch sizes have been provided.

The drug product manufacturing process together with the in-process controls has been adequately described. The processes are standard manufacturing processes for the production of parenterals and include sterile filtration, aseptic filling, lyophilisation and labelling and packaging.
In-process controls and the corresponding acceptance criteria are described. Maximum process times and condition have been set for all critical steps performed at other temperatures than the proposed storage conditions. The times are adequately supported by data.
Validation
The critical steps in the manufacture of the medicinal product have been validated. These include sterile filtration, steriliation of equipment and lyophilisation.

- Drug Product Specification

Drug product specifications for release and end-of-shelf life have been submitted. The specification includes identity tests, purity tests and assays.

- Batch Analysis Data

Batch analysis data has been presented. All batches met the specifications.

- Container Closure System

The components of the container-closure system of the drug product are described in the section *Composition* of this report.

- Stability of the Product

Stability data for the drug product was generated from ongoing extensive stability studies.
All submitted real time/real temperature stability data met the specifications. In summary, the submitted stability data support the proposed shelf life of 24 months at 2-8^{o}C .
The submitted stability documentation on the diluent in the prefilled syringe was considered acceptable to support a shelf-life of 24 months.

Adventitious Agents Safety Evaluation

The viral safety of Raptiva has been adequately investigated and is sufficiently justified.

Furthermore the safety of Raptiva with regard to other adventitious agents (including TSE) has been sufficiently assured.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application demonstrated consistent batch-to-batch production of Raptiva achieving a defined quality for the drug substance and the drug product. The cell culture and purification of the drug substance, efalizumab, are adequately controlled and validated. Appropriate drug substance specifications have been set. The drug substance has been well characterised with regard to its physicochemical and biological characteristics using state-of the-art methods. The manufacturing process of the drug product has been described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications. The viral safety and the safety concerning other adventitious agents (including TSE) have been sufficiently assured. On the basis of the data provided and the agreed follow-up measures, the quality of the product is satisfactory for the grant of a Marketing Authorisation.

3. Part III: Toxico-pharmacological aspects

Introduction

Efalizumab does not cross-react with CD11a from species other than humans and a non-human primate. Therefore, conventional non-clinical safety data with the medicinal product were limited.

Non-clinical *in vivo* assessments of efalizumab per se were confined to a non-human primate. A number of constraints prevented a full histopathological evaluation which limited the value of the studies carried out to determine the safety of efalizumab.

To have a more comprehensive safety evaluation, muM17, a chimeric rat/mouse anti-mouse CD11a antibody, was developed as a surrogate for efalizumab.

Pharmacology studies of efalizumab were undertaken *in vitro* with human and non-human primate lymphocytes, and *in vivo* in a non-human primateas part of ADME and safety studies. *In vitro* and *in vivo* pharmacology studies were also conducted with muM17 in mice to evaluate the acceptability of this antibody as a surrogate for efalizumab.

Intravenous (IV) and subcutaneous (SC) pharmacodynamic/pharmacokinetic (PK/PD) studies of efalizumab were conducted in a non-human primate, and IV and SC PK/PD studies of muM17 were conducted in mice. Safety pharmacology parameters were incorporated in repeat dose toxicity studies with efalizumab and muM17.

In addition, rabbits were used to assess pharmacokinetic comparability of the XOMA and Genentech-manufactured efalizumab.

Efalizumab was evaluated in non-human primate IV toxicity studies of up to 6 months duration. In mice, repeat dose SC toxicity studies of up to 4 weeks duration, including an immunotoxicity study, were conducted with muM17. A 6-month muM17 study in a lymphoma-susceptible mouse strain was conducted.

A full reproductive toxicity testing program was conducted with muM17 SC in mice, together with a battery of immunological assays on offspring.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

All *in vitro* assays with efalizumab were performed utilising human lymphocytes, and animal pharmacology studies with efalizumab were performed in a non-human primate. Similar studies in mice cells or mice evaluated the *in vitro* and *in vivo* pharmacological activities of the mouse chimeric antiCD11a antibody muM17.

Studies on the mechanism of action for efalizumab and muM17 showed that the interaction of efalizumab and muM17 with CD11a on leukocytes of 3 species is specific and leads to cellular uptake and degradation of CD11a by T lymphocytes. Consequently CD11a is down-modulated on the plasma membrane of these T lymphocytes, which are no longer able to be activated by α-CD3 antibodies, as detected by expression of CD69. These effects are concentration dependent. The down-modulation of CD11a on leukocytes leads to a hampered interaction with intercellular adhesion molecule-1 (ICAM-1) and blocks the migration of T-lymphocytes across human vein endothelial cells (HUVEC) in a concentration dependent manner. The lowered expression of CD11a on T-lymphocytes also blocks the interaction with human keratinocytes.

In vivo a down-modulation of CD11a on lymphocytes is found and similar effects to what is described for the in vitro experiments on the interaction with ICAM are observed. Furthermore extravasation of lymphocytes into the tissue is inhibited which leads to an altered trafficking of leukocytes, resulting in increased peripheral White Blood Cell (WBC) counts. The effects, described in vivo, disappear after stopping administration of the drug substance.

Currently, no naturally occurring animal models of psoriasis exist. A model has been developed using human psoriatic skin grafted to SCID mice. In SCID-skin mice model, indications are obtained that efalizumab should have an ameliorating effect on psoriatic skin.

A comparison of binding characteristics of efalizumab manufactured at the two different manufacturing sites, Genentech and XOMA, to human and a non-human primate lymphocytes showed that efalizumab from either site binds with similar affinity to CD11a on human and non-human primate T lymphocytes.

The pharmacodynamics were further investigated in pharmacokinetic and toxicology studies.
In a non-human primate, down-modulation of CD11a, occurred within 24 hours after dose administration of 2 mg/kg subcutaneous (SC) or 0.5 mg/kg intravenous (IV) or above. As long as the plasma efalizumab concentration stayed above 1-10µg/ml the CD11a receptor remained almost completely occupied and the receptor was effectively down-modulated (80-95%). When treatment of the animals is discontinued, CD11a expression is increased to levels above pretreatment, suggesting a risk for rebound effect.
In mice similar pharmacodynamics were observed after SC administration of muM17. The pharmacodynamic effect of a SC dose of 3 mg/kg/week muM17 in mice was equivalent to that of a SC dose of 1 mg/kg/week efalizumab in humans.

- Secondary pharmacodynamics

Both the humoral response to some antigens and the cell-mediated response were inhibited: the primary antibody-response in a non-human primate to tetanus toxoid and primary and secondary response in mice to sheep red blood cells were hampered, and, in mice an inhibition of the delayed type hypersensitivity (DTH) was observed. In the peri/postnatal reproduction toxicity study, a reduced primary antibody response was also seen in F_1 mice up to at least 11 weeks of age.
Cross-reactivity with other cell types, amongst which glial cells and stromal cell, belonging to the immune system, was observed.

- Safety pharmacology

Core safety endpoints were incorporated into the repeat dose non-human primate studies. The core safety pharmacology observations did not indicate any concern.

- Pharmacodynamic drug interactions

No formal non-clinical drug interaction studies have been performed with efalizumab or muM17. As efalizumab and muM17 bind specifically to CD11a-bearing cells, plasma protein binding, cytochrome P450 metabolism, conjugation reactions, P-glycoprotein transport and renal filtration are unlikely to be affected by efalizumab.

Nevertheless, co-administration of drugs that affect lymphocyte number and activity or the expression of CD11a could likely affect both the PK and PD of efalizumab. The effects of efalizumab on the immune system may be potentiated by other immunosuppressives used for psoriasis treatment.

- Summary of findings

Efalizumab is a recombinant humanized monoclonal antibody that binds specifically to the CD11a subunit of LFA-1 (lymphocyte function-associated antigen-1), a leukocyte cell surface protein. By this mechanism, efalizumab inhibits the binding of LFA-1 to ICAM-1, which interferes with T lymphocytes adhesion to other cell types. LFA-1 is present on activated T lymphocytes, and ICAM-1 is up-regulated on endothelial cells and keratinocytes in psoriasis plaques. By preventing LFA-1/ICAM binding, efalizumab may alleviate signs and symptoms of psoriasis.
When treatment of non-human primate is discontinued, CD11a expression is increased to levels above pretreatment, suggesting a risk for rebound effect. Nonclinical data have only limited contribution in predicting these effects in human; therefore attention should be paid to clinical data.
Efalizumab inhibits both the humoral response to some antigens and the cell-mediated response. In mice an inhibition of the delayed type hypersensitivity (DTH) was observed.
The effects of efalizumab on the immune system may be potentiated by other immunosuppressives.

Pharmacokinetics

Enzyme-linked immunosorbent assays (ELISA) were developed and used for measuring efalizumab in a non-human primate and rabbits, muM17 in mice, and anti-drug antibodies in these species.

- Absorption- Bioavailability

Maximal plasma concentrations after SC administration of either efalizumab in a non-human primate or muM17 in the mouse were obtained within 0.5-2 days. Bioavailability was dose dependent and comparable.

- Distribution

Distribution studies in mice suggested that in binding species, efalizumab and muM17 distribute mainly to the interstitial space, vascular space, and tissues known to express CD11a. In non-binding species, efalizumab distributes to interstitial and vascular spaces. In binding species, the distribution is predominantly due to binding to CD11a. However, distribution was studied in CD-1 mice with the rat anti-mouse anti-CD11a antibody M17, disregarding the possible influence of the Fc-moiety on the distribution of the antibody. In blood, ^{125}I-M17 bound to leukocytes and platelets as anticipated based on the known cellular distribution of the antigen. Specific uptake of radioactivity was observed in spleen, liver, bone marrow and lymph node. Again, in these organs radioactivity was associated with leukocytes.
In mice the antibody muM17 crosses the placenta and is excreted into milk.

- Metabolism and excretion

The disposition of efalizumab in the non-human primate studied is thought to be determined by both the specific saturable CD11a-mediated clearance and the nonspecific high-capacity Fc-mediated IgG clearance pathways. CD11a-mediated clearance of muM17 in the mouse was demonstrated in mice on a cellular level. Plasma pharmacokinetic data obtained in both species are consistent with the view of a saturable CD11a receptor-dependent non-linear PK at low doses and a linear Fc-mediated PK a higher doses. In the rabbit only the latter is accountable for the disposition of efalizumab. The CD11a receptor-dependent non-linear PK leads to higher clearance and shorter $T_{½}$ at low doses as compared to high doses.

The pharmacokinetics of efalizumab in a re-exposure study were similar to those observed in other PK studies. Development of an antibody response led to more rapid clearance, as would be expected.
Antibodies after first exposure did not appear to affect the PD or PK, but after the second exposure, antibody titers were higher, efalizumab clearance was faster, and the pharmacological effects appeared to reverse faster than in the other animals.

- Comparability

Pharmacokinetic and pharmacodynamic comparability of XOMA material that was used in the non-clinical safety studies and Genentech material that is intended for marketing was investigated. Overall, the data are too limited to draw firm conclusions, however, the results obtained did not lead to any unexpected results which could lead to any issues regarding comparability of the two materials being raised.

Toxicology

- Single dose toxicity

After a single administration of muM17 to female mice, the maximum non-lethal dose was > 50 mg/kg. The only observed effect was an increase in white blood cell counts.

- Repeat dose toxicity

Among the studies, different formulations were used. In repeat-dose studies in a non-human primate a liquid formulation not intended for marketing was used. In addition, the route of administration was the intravenous one, whereas the clinical route will be subcutaneous.

In treated animals, an inhibitory effect on the humoral response to a tetanus toxoid immunisation was observed. The humoral response to tetanus toxoid immunisation occurred at lower levels and later in time in treated animals than in control animals. One animal died of infection. In the lymph nodes of treated animals, paracortical atrophy was observed, accompanied by a decrease in CD3+ cells. This observation was consistent with the decreased cellularity, which was observed in lymph nodes of mice (see below). The effect decreased upon recovery. Among CD4+ and CD8+ subsets in blood, there was a slight increase in the proportion of CD4+ cells.
Two of 33 animals developed detectable anti-efalizumab antibodies. No apparent adverse effects were noted. However, a previously mounted immune response affects pharmacokinetics – as demonstrated in a re-exposure study. Efficacy may also be affected.
Legal and ethical restraints related to the species used in the toxicity studies justify the absence of histopathological data. Instead, histopathology data are available from the 26-week p53 +/+ wild-type mouse study (see below).
In repeat-dose studies in mice, muM17 was administered.
Increased counts of white blood cells, lymphocytes, eosinophils, neutrophils and monocytes in blood, increased spleen weight, histological changes in the spleen, and decreased cellularity in lymph nodes may be associated with the pharmacological activity of muM17, resulting in altered trafficking of white blood cells.
As in the other species studied, inhibitory effects on the immune system were observed. A sharp but reversible decrease was shown in the primary antibody (IgM) forming cell response to exposure to sheep red blood cells. The secondary response (IgG) was not significantly reduced. Natural Killer cell activity was decreased at all doses. In males, this effect was still visible after a 4-week recovery period. Spleen lymphocytes were increased, with corresponding increases in CD4+ cells in males, and in CD8+ in females.
Anti-muM17 antibodies were detected in 2 out of 342 mice, with no apparent adverse effects.

- Genotoxicity

No genotoxicity studies were performed, since these are not needed according to the ICH Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

- Carcinogenicity

Carcinogenic potential and long-term toxicity of muM17 was tested in a 26-week study using $p53^{+/+}$ wild-type mice. No evidence of carcinogenicity was seen in this study. The study was limited to six months and so the results should be interpreted cautiously. Even though, it has previously been shown that cyclosporin can induce tumours in the wild type p53 mouse within 6 months, a duration of 6 months is still rather short for a genetically non-modified mouse model. Therefore negative result of the study should be taken with reservation. Immunological effects observed in this study were similar to those in the repeat-dose toxicity studies. In addition, platelet counts were decreased, an effect that was more prominent in females than in males. Histopathology did not reveal any other untoward effects.

- Reproductive and developmental studies

Reproductive and developmental toxicity was investigated in mice, using muM17.
There were no effects on reproduction and fertility parameters. The parental effects that were observed were also shown in the repeat-dose studies. A number of observations may be associated with the pharmacological activity of muM17, like decreased cellularity in lymph nodes and histological changes in the spleen. Further, the number of antibody forming cells in response to exposure to sheep red blood cells was reduced by 95-99%.
MuM17 crossed the placenta of pregnant mice. No treatment-related effects on embryo-foetal development were observed after administration of muM17 to mice up to 30 mg/kg/week.
In a pre- and postnatal study in mice, it was shown that in the offspring (F1), the antibody forming cell response to exposure to sheep red blood cells was reduced, indicating a decreased T-cell dependent immunity in pups caused by exposure to muM17 in utero and/or via the milk. This effect was visible

at 11 weeks of age. At 25 weeks of age, it was no longer significant indicating that it is a transient effect. There were no treatment-related effects on reproductive parameters in F0 and F1 mice, on the development of F1 mice and no visible effects on F2 pups. Increases in spleen weight were observed in F1 animals, which are likely associated with the pharmacological activity of muM17. In blood of F1 animals, there was a relative increase in CD4+ cells and a relative decrease in CD8+ cells.
The NOAEL in the fertility and embryo/foetal toxicity studies for general reproductive and embryo/foetal parameters was 30 mg/kg/day and the 3 mg/kg/day dose is pharmacologically as potent as the therapeutic dose of 1 mg/kg in humans. Therefore, the ratio of the plasma exposures observed at these two doses was considered to represent a safety margin, being >10.

- Local tolerance

In the 26-week non-human primate study, no gross evidence of irritation or contact sensitisation at the infusion site was noted during the study in any animal.

- Other toxicity studies

Studies on juvenile toxicity were not conducted since Raptiva has only been developed and is only indicated for adult patients.

- Summary of findings

In the toxicology studies, overall, efalizumab and muM17 were generally well tolerated up to 26 weeks at the highest doses tested, 40 mg/kg/week (IV) in a non-human primate and 30 mg/kg/week (SC) in mice, respectively. The main effects seen in the toxicology studies were those related to the pharmacology of the antibody. The primary pharmacological effect on receptor level, i.e. down-modulation of the CD11a receptor was seen in all studies. In all pivotal studies, there was a full pharmacologic effect already at the low dose. Higher dosages did not result in stronger effects. Besides impairment of transendothelial trafficking, reduced adhesion of lymphocytes and other pharmacological effects leading to the therapeutic effect resulting from the down-modulation of CD11a, other immunological responses were noted that are likely related to the down-modulation of CD11a, but may be considered adverse. Notably, antibody response to artificial antigens – tetanus toxoid or sheep red blood cells – was severely diminished, indicating an impaired immune function. A potential exacerbation of infection by efalizumab cannot be ruled out.
In pups of mice treated with an antibody analogue of efalizumab, a decrease in T-cell dependent immunity was observed up to at least 11 weeks of age. Only at 25 weeks of age this decrease was no longer significant. No safety margin exists and warning referring to this effect should be included in section 5.3 of the SPC. Pregnant women should not be treated with Raptiva.

Discussion on the non-clinical aspects

Efalizumab binds specifically to the CD11a subunit of LFA-1. By preventing LFA-1/ICAM binding, efalizumab may alleviate signs and symptoms of psoriasis.Efalizumab does not cross-react with CD11a from species other than humans and a non-human primate. Therefore, conventional non-clinical safety data with the medicinal product are limited and do not allow for a comprehensive safety assessment.Efalizumab inhibits both the humoral response to some antigens and the cell-mediated response. In mice treated with the murine surrogate antibody muM17, an inhibition of the delayed type hypersensitivity (DTH) was observed.The 6-month repeated dose study in a non-human primate is of limited value due to a number of constraints. Nevertheless, animals appear to have been sufficiently exposed to cause long-term down-modulation of CD11a and the potential effects of this long-term change were evaluated in the study to some extent. In addition the lack of histopathological data is partly compensated by p53 +/+ wild-typea 26-week study in mice with the surrogate antibody muM17. Studies did not produce results that would prevent use of efalizumab in humans.
No evidence of carcinogenicity was seen. Yet, the results should be seen with some reservation, because the duration of the study was only 6 months. Immunological effects observed in this study were similar to those in the repeat-dose toxicity studies of shorter duration. In addition, platelet counts

were decreased.In pups of mice treated with an antibody analogue of efalizumab, a decrease in T-cell dependent immunity was observed. Pregnant women should not use Raptiva and women of childbearing potential should be advised to use appropriate contraception.Immunoglobulins are expected to be excreted in human milk and an antibody analogue of efalizumab was shown to be excreted in milk of mice, therefore women should not breastfeed during treatment with Raptiva.Further reassurance of the safety of efalizumab should be obtained from long-term safety data in humans.

4. Part IV: Clinical aspects

Introduction

Seven phase I studies, 2 phase II studies and 7 phase III studies were submitted, including five pivotal clinical studies evaluating efficacy of efalizumab primarily as monotherapy versus placebo.
All studies were carried out in patients with moderate to severe plaque psoriasis, except two bioequivalence studies (ACD2389g and ACD2617) in healthy volunteers, one study in patients with a primary renal transplant and one phase II study in patients with allergic asthma.
Studies used efalizumab manufactured by either XOMA Ltd. (XOMA efalizumab) or Genentech, Inc. (Genentech efalizumab). XOMA conducted the Phase I and II studies except ACD2389g, and Genentech conducted all Phase III studies except for 24011 conducted by Serono.

3291 patients have received efalizumab (3186 s.c.) during the development programme:

2651 patients	12 weeks
1053 patients	24 weeks
221 patients	48 weeks
158 patients	108 weeks

The overall exposure was 2,500 patient-years.

All clinical trials were stated to have been conducted in accordance with "good clinical practice" (GCP).

Pharmacokinetics

A number of analytical methods have been used to characterise the pharmacokinetics and pharmacodynamics of efalizumab: assays to assess the plasma concentrations of efalizumab, assays to assess the pharmacodynamics of efalizumab, and assays to assess anti-efalizumab antibodies.

- Absorption – Bioavailability

Absorption has been studied in healthy subject and in the target population following both single-dose and steady-state i.v. and s.c. administration.
After subcutaneous administration of efalizumab peak plasma concentrations are reached after 1 – 2 days, indicating a slow release of efalizumab from injection site. Comparison with intravenous data indicated an average bioavailability of about 41% at the recommended dose level of 1.0 mg/kg/wk. Non-linear pharmacokinetics are observed due to the saturable receptor-mediated clearance. There is a large inter-individual variability (up to 100%) taking into account the whole dose range studied, but at a dose level of 1 mg/kg/wk variability is about 60-70%.
Steady state was achieved at week 4. At the 1mg/kg/wk dose level (with an initial dose of 0.7 mg/kg the first week as conditioning phase), mean efalizumab plasma trough values ranged between 5.3 – 11.1 µg/ml. The elimination half-life was about 5 – 7 days.
The s.c doses were administered into the upper arms, buttocks, abdomen, and thighs. Site of injection most probably do not impact on the exposure of efalizumab. Based on common medical practice, the site of injection was rotated in pivotal Phase III studies and rotating the site is recommended in the summary of product characteristics.

Subjects who developed antibodies to efalizumab (HAHA) showed an apparently reduced efalizumab exposure, however it appeared that this reduction did not affect the CD11a down-modulation and saturation of available binding sites.

- Comparability of formulations

Early clinical studies were conducted with efalizumab in a 4 mg/mL liquid formulation for intravenous (i.v.) administration produced by XOMA. In addition, to support subcutaneous (s.c.) dosing, a lyophilised formulation was developed by XOMA that could be reconstituted at 100 mg/mL. After development the product was transferred to Genentech and further developed. Although a higher exposure was observed for the Genenetech formulation, further studies showed that the difference in pharmacokinetics seems to be of no pharmacodynamic relevance.

- Distribution

Measurements of volume of distribution of the central compartment after single intravenous doses were 110 ml/kg at dose 0.03 mg/kg and 58 ml/kg at dose 10 mg/kg.

- Metabolism and excretion

The expected products of the metabolism of biotechnology-derived proteins and peptides, including IgG1 monoclonal antibodies such as efalizumab, are small peptides and individual amino acids. Cytochrome P450 enzymes as well as conjugation reactions are not involved in the metabolism of efalizumab. The metabolism of efalizumab is through internalisation followed by intracellular degradation as a consequence of either binding to cell surface CD11a or through bulk fluid phase endocytosis and failure to bind to FcRn, the IgG salvage receptor, within the endosome. If efalizumab does not associate via its Fc domain with FcRn in the endosome, the antibody is directed to the lysosome for degradation to small peptides and amino acids. Conversely, if efalizumab's Fc binds FcRn within the endosomes, the antibody is recycled back into circulation.
The elimination half-life was about 5.5-10.5 days at 1 mg/kg/day subcutaneous. T_{end} at steady state is 25 days (range 13-35 days). Efalizumab is cleared by nonlinear saturable elimination (dose dependent). The terminal half-life increases from low to high doses, reflecting elimination mediated mainly by the specific saturable CD11a receptors, the non specific high-capacity FcRn receptors (IgG salvage receptor), standard Fcγ receptors, or other nonspecific protein clearance mechanisms on reticuloendothelial cells.
It appeared that the receptor mediated clearance of efalizumab was saturated when plasma efalizumab concentrations were above 1 µg/ml. Levels of CD11a expression on CD3+ lymphocytes (Tcells) were (maximal) reduced for 70 – 80% in case an i.v. dose was used above 0.3 mg/kg/wk or a s.c dose of 1 mg/kg/wk or higher. Regardless the dose administered, levels remained reduced as long as efalizumab plasma concentrations remained above 1 µg/ml. When efalizumab plasma levels decreased below 1 µg/ml, the drug was rapidly cleared from the circulation and expression of CD11a returned to normal within 7 – 10 days thereafter.

- Special populations

Specific pharmacokinetic studies in patients with renal or liver impairment, and children have not been conducted and this information is included in the summary of product characteristics. Taking into account the metabolism of efalizumab, it is not expected that the pharmacokinetics of efalizumab in patients with renal or hepatic impairment will be clinically significant influenced but Raptiva should be used with caution in this patient population.
A population pharmacokinetic analysis of efalizumab was performed with a base model assuming linear PK model. The model predicted a 24% decrease in CL/F in patients receiving 2 mg/kg/week thus confirming the nonlinear PK of efalizumab. The results suggest that weight is the single important predictor of efalizumab PK, while the effects of other covariates age, baseline PASI score and baseline lymphocyte count were modest.
No clinical program to evaluate the safety and efficacy of efalizumab in children was planed at the time of CHMP assessment.

- Interaction studies

There have been no formal drug interaction studies performed with Raptiva.
The plasma clearance of efalizumab was arround 50% lower in renal transplant patients, receiving cyclosporine/sirolimus/prednisone therapy or cyclosporine/mycophenolate mofetil/prednisone.
Given the mechanism of action of efalizumab, its effects on the immune system may be potentiated by immunosuppressives commonly used for the treatment of psoriasis.
Raptiva has not been studied in combination with immunosuppressive systemic antipsoriasis medicinal products. Therefore, combination therapies with these products are not recommended.
Raptiva has been used in combination with topical corticosteroids in psoriasis patients without any untoward effects nor with any observable significant beneficial effect of the combination therapy above monotherapy with efalizumab.

Pharmacodynamics

- Mechanism of action

Binding of CD11a by efalizumab results in saturation of available CD11a binding sites and down-modulation of cell surface CD11 expression. This event is believed to decrease the activity of lymphocytes and reduce their translocation to peripheral tissues (such as in psoriatic plaques).
Efalizumab blocked the interaction of human T-lymphocytes with tissue-specific cells (e.g., human keratinocytes) in a concentration-dependent manner.

- Primary and Secondary pharmacology

Several pharmacodynamic studies (phase I-II) including also dose response investigations were provided that explored the mechanism of action and required dose to attain optimal pharmacodynamic effects and clinical efficacy. Pharmacodynamics evaluation was also included in the phase III trials.
Multiple IV doses ≥0.3 mg/kg/wk were required to maintain CD11a down-modulation between weekly doses, whereas doses ≥0.6 mg/kg/wk were required to maintain full CD11a saturation between weekly doses. Two Studies (HUPS254 and HUPS256) provided PK/PD data after multiple SC doses of efalizumab of 0.5, 1.0, 1.5, 2.0, and 4.0 mg/kg/wk for 8-12 weeks in subjects with psoriasis. Maximal PD effects were seen 24-48 hours after the first dose, compared with 4-24 hours after IV dosing in Study HU9602.
Following the 12th and last dose of 1.0 mg/kg/wk SC, CD11a expression returned to baseline as efalizumab was cleared from circulation. Between 5 and 8 weeks following the last dose, CD11a expression was within 25% of baseline values. At the end of the follow-up period (12 weeks after the last dose), average CD11a expression and available binding sites had increased to above baseline levels in the 2.0 mg/kg/wk group (174% ± 98% of baseline expression) but not in the 1.0 mg/kg/wk group (72% ± 15% of baseline expression). The cause or clinical relevance of this above-baseline CD11a expression is currently unknown, but the finding is in line with the results of the animal studies.
Overall, SC doses > 1.0 mg/kg/wk did not appear to produce additional histologic changes in terms of epidermal CD11a saturation, thickness, dermal and epidermal T-lymphocyte numbers, and keratin 16 (K16) expression, despite higher circulating levels. Maximal effects on CD11a were good indicators of adequate dosing but were not useful as predictors of clinical response at doses of 1.0 and 2.0 mg/kg/wk SC for 12 weeks.

Of all PK/PD evaluable subjects (from 11 studies) who were tested for anti-drug antibody titers against efalizumab in these studies, 85 were found to be positive. A conservative estimate based on the subset of subjects with adequate follow-up after discontinuation leads to an estimate of 6.3%. The absolute number of patients presenting anti-efalizumab antibodies remained too limited to allow definitive conclusions in terms of the effect on efficacy and safety, such as possible neutralising capacity. Limited data from long-term treatment in the ongoing trial ACD2243g seem to confirm the estimate of the occurrence of antibodies to efalizumab to be approximatelly 6%. However, the

sensitivity of the assay for neutralising antibodies is limited. The applicant should try to develop more sensitive assay in addition to the intended post-marketing monitoring for adverse drug effects in patients with antibodies to efalizumab.
Absolute white blood cell (WBC) count increased by 2.5-3.5x10^3 cells/mm^3 to reach approximately 10x10^3 cells/mm^3 following 1.0 or 2.0 mg/kg/wk efalizumab. The time course, extent, and reversal of lymphocyte increases closely followed the patterns observed in the PD markers of CD11a expression and available CD11a binding sites. Following the 12th and final dose of 1.0 mg/kg/wk SC efalizumab, lymphocyte levels returned to within 10% of baseline by 8 weeks post last dose.

Available data suggest that a mild, general inflammatory reaction occurs after the initial administration of efalizumab in humans. The changes in cytokines and acute phase reactants detected in subjects and the responses of cells to efalizumab *in vitro* suggest that the first-dose effect is not caused by activation of T-lymphocytes.

Available data suggest also that primary immunisation may not be effective during efalizumab treatment. (A trend toward reduced IgG levels after rechallenge with ϕX174 on Day42 was observed in one study). The SPC states that subjects should not receive acellular, live and live-attenuated vaccines during efalizumab treatment.

The maintenance of a secondary humoral immune response was tested by measuring serum tetanus antibody levels in subjects before and after receiving a single IV dose of efalizumab. The results suggest that subjects were able to maintain a pre-existing secondary humoral immune status after single and multiple doses of efalizumab.
The results of studies on cell-mediated immunity, as assessed by intradermal challenge with tetanus toxoid, suggest that established T-lymphocyte-mediated immune responses persist despite efalizumab treatment.
No relevant changes in CMV antibody levels were found during efalizumab treatment indicating that baseline immune response is maintained their throughout the entire study and that there is minimal risk of new or re-activated CMV infections.

Overall, the PK/PD data are extensive although certain areas are not totally elucidated. The pharmacodynamic rationale for the treatment with efalizumab in the sought indication at the recommended dose level is supported by the provided data.

Clinical efficacy

- Dose response studies

Data presented from a number of Phase I efalizumab studies show that improvement in psoriasis disease as assessed by histology was seen at an IV dose of 0.3 mg/kg/wk and at SC doses of ≥ 1.0 mg/kg/wk. SC doses > 1.0 mg/kg/wk did not appear to produce additional histologic changes in terms of epidermal CD11a saturation, thickness, dermal and epidermal T-lymphocyte numbers, and keratin 16 (K16) expression, despite higher circulating levels. Together, the clinical pharmacology of efalizumab and the safety and efficacy data (including phase III studies with 1.0 mg/kg/wk or 2.0 mg/kg/wk) support the selection of 1.0 mg/kg/wk SC as the optimal dose for efalizumab.

- Main studies

Main clinical trials conducted in patients with moderate to severe plaque psoriasis are presented below:

Study number Phase	Study Design	Number of subjects entered/completed	Duration of treatment
ACD2058g Phase III Double-blind	Efalizumab XOMA subcutaneously, 1.0 mg/kg/wk 2.0 mg/kg/wk Placebo	 162/149 166/145 170/151	12–24 WEEKS
ACD2059g Phase III Double-blind	Efalizumab XOMA or GNE subcutaneously, 1.0 mg/kg/wk 2.0 mg/kg/wk Placebo 2nd 12 wk: 2.0 mg/kg/wk or 2.0 mg/kg/wk or 4.0 mg/kg/wk or placebo	 232/211 243/227 122/111	12–24 WEEKS
ACD2390g PHASE III Double-blind	Efalizumab GNE subcutaneously 1.0 mg/kg/wk Placebo	 369/345 187/175	12 weeks
ACD 2600G Phase III Double-blind	Efalizumab GNE subcutaneously 1.0 mg/kg/wk Placebo	 450/421 236/218	12 weeks
IMP 24011 Phase III Double-blind	Efalizumab GNE subcutaneously 1.0 mg/kg/wk Placebo	 529/476 264/247	12 weeks

In addition, there were an open-label (extension) studies; ACD 2243g, ACD2062g and ACD2391g.
Five of these studies (ACD2058g, ACD2059g, ACD2390g, ACD2600g, and IMP24011) were randomised, double blind, placebo-controlled, Phase III trials using efalizumab administered subcutaneously (SC) and are considered as pivotal trials. These phase III placebo-controlled trials with efalizumab were similarly designed. Inclusion and exclusion criteria were comparable. The differences involved greatly the dose regimen and follow-up evaluations RT (re-treatment) or ET (extended treatment). The primary endpoint concerned efficacy PASI75 measurement. Safety was a secondary endpoint, except in study ACD2600g where endpoints were vice versa. Studies ACD2058g, ACD2059g and ACD2390g are presented together before presentations of studies ACD2600g and IMP24011, which were later submitted.

Studies ACD2058g, ACD2059g and ACD2390g

METHODS

Study Participants
Patients enrolled in the pivotal studies were subjects with moderate to severe plaque psoriasis.
Main Inclusion criteria were:
- Diagnosis of plaque psoriasis for 6 months,
- Minimum Psoriasis Area and Severity Index (PASI) score of 12.0 at screening,
- Plaque psoriasis covering ≥10% of total body surface area (BSA),Candidate for systemic treatment.

Main Exclusion criteria were:
- History of or ongoing infections.
- Presence or history of malignancy,
- HIV
- Pregnancy or lactation
- History of severe allergic or anaphylactic reactions to humanised monoclonal antibodies.

Treatments
For the 12-week FT (first treatment) period in Studies ACD2058g and ACD2059g, subjects received either 1.0 mg/kg/wk or 2.0 mg/kg/wk SC efalizumab or placebo. Subjects from Study ACD2390g were randomised in a 2:1 ratio to receive either 1.0 mg/kg/wk SC Genentech efalizumab or matching placebo for 12 weeks (FT period). The only allowed concomitant psoriasis treatments were emollient cream, tar or salicylic acid preparations for the scalp, and low-potency (Grade VI–VII) topical corticosteroids for lesions on the face, hands, feet, axillae, or groin.

Objectives
Primary objectives:
- To assess the efficacy of weekly subcutaneous dosing of efalizumab 1.0 or 2.0 mg/kg in patients with moderate to severe psoriasis versus placebo as measured by the proportion of subjects achieving ≥ 75% decrease from baseline in PASI at the end of the initial 12 week treatment period (First Treatment or FT Day 84).
- Safety and tolerability of 12 weekly subcutaneous dosing of efalizumab 1.0 or 2.0 mg/kg versus placebo.

Secondary objectives:
- To assess the efficacy of weekly subcutaneous dosing of efalizumab 1.0 or 2.0 mg/kg measured by secondary endpoint (discussed below) versus placebo.
- Efficacy and safety of a second 12-week course initiated at the time of relapse of efalizumab versus placebo.
- Duration of response.
- Time course of response.
- In partial and non responders the following were assessed: safety and tolerability of 24 weeks of efalizumab, efficacy of 24 weeks continuous efalizumab therapy and duration of response following a 24-week course of efalizumab.
- In study ACD2390g: steady-state pharmacokinetics and pharmacodynamics.

Outcomes/endpoints
The primary efficacy endpoint in the Phase III trials was the proportion of subjects who had ≥75% improvement in PASI score (a PASI-75 response) from baseline when assessed 1 week after the last of 12 weekly doses of efalizumab.

Secondary endpoint for all three studies included:
- The proportion of subjects achieving an Overall Lesion Severity (OLS) rating of Minimal or Clear,
- Mean improvement in the Itching Scale (a patient-reported measure),
- The proportion of subjects with a Physician's Global Assessment (PGA) rating of Cleared or Excellent,
- Mean improvement in the thickness component of the PASI score,
- Mean improvement in the percentage of BSA affected by psoriasis.

Other pre-specified secondary efficacy endpoints in Study ACD2390g included the proportion of subjects with ≥50% improvement in PASI score relative to baseline after 12 weeks of treatment (known as PASI-50), mean percent PASI improvement over time, mean improvement in the Dermatology Life Quality Index (DLQI), and mean improvement in the frequency and severity subscales of the Psoriasis Symptom Assessment (PSA).

All outcomes were measured at 12 weeks of treatment and were compared with baseline, with the exception of OLS, which is a static measure.
Sample size
The estimation of power for efficacy assumed PASI-75 response rates of 20 to 25% in efalizumab treatment groups versus placebo response rates of 2 to 5%."

Randomisation and blinding (masking)
For studies ACD2058g and ACD2059g patients and investigators were blinded for which treatment the patients received (efalizumab or placebo). However the dose level was not blinded for the patients.

For study ACD2058g the subjects were randomly assigned to low-dose efalizumab, high-dose efalizumab, low-dose placebo and high-dose placebo in a 2:2:1:1 ratio for the first 12 weeks (FT).
For study ACD2059g the subjects were randomised in a 4:4:1:1 ratio to high dose efalizumab, low dose efalizumab, high dose placebo and low dose placebo for the first 12 weeks.
Study ACD2390g was a double-blind study and the subjects were randomised to receive low dose efalizumab or placebo in a 2:1 ratio.
Statistical methods
In studies ACD2058g and ACD2059g two treatment comparisons were of interest during the FT period of this study: 1.0 mg/kg efalizumab versus placebo and 2.0 mg/kg efalizumab versus placebo. The placebo groups for each of the two dose levels were combined for all statistical comparisons following investigation of baseline comparability of the two placebo groups.
All statistical tests were two sided. Except where noted, evaluation of continuous variables was performed using analysis of variance (ANOVA); ANOVA was to be replaced by the nonparametric counterpart if normality assumptions were severely violated.

Results
Participant flow and Baseline data

Study no	Screened	Randomised	Percent
ACD2058g	675	498	26.2
ACD2059g	911	597	34.5
ACD2390g	771	556	27.9

Study ACD2058g consisted of 2 12-week treatment periods: First treatment (FT), and then retreatment (RT) or extended treatment (ET). There were 2 observation periods without treatment: Observation period (OB) and Follow-Up (FU).

On FT Day 84 subjects were defined as responders, partial responders, or non-responders according to the following definitions:

- Responder: PASI decreased ≥ 75% from FT day 0
- Partial responder: PASI decreased ≥ 50% but < 75% from FT day 0
- Non-responder: PASI decreased < 50% from FT day 0

Study ACD2059g consisted of 3 periods: First treatment (FT), extended treatment (ET) and Follow-Up (FU). The 434 patients that have been treated with efalizumab during the FT period and go into extended treatment are further classified as the ET-A subjects. ET-AR are the responders, ET-AP are the partial responders and ET-AN are the non-responders. For definitions about responders, partial responders and non-responders, see under study ACD2058g.

Study ACD2390g consisted of 1 treatment period of 12 weeks. After completion of this trial, all subjects could transfer to open-label study ACD2391g. Subjects who discontinued early from this study were to transfer to study ACD2391g for follow-up.

In studies ACD2058g, 2059g and 2390g, there were far more male (between 64,8 % and 72,3 %) than female included in these studies but the groups were comparable regarding gender distribution. More whites (between 84,9 % to 91,6 %) than coloured people were included in all treatment groups. For the other characteristics there were no meaningful differences. However, in study ACD2058g the proportion of patients with prior systemic therapy was lower (54.8%, all subjects) in all the groups than in study ACD2059g (66.7%, all subjects) and study ACD2390g (75.9%, all subjects). For the other characteristics there were no significant differences between the studies.

Numbers analysed
The ITT population consisted of all subjects who were randomised into the FT period, whether or not they received any study drug or completed the full course of treatment.

Outcomes and estimation
Results of the first treatment period are provided in the table below.

First treatment period – Primary Efficacy Endpoint and principal secondary efficacy endpoint

Study No.	Manufacturer/ Route/ Treatment Group	Number Enrolled/ Completed [a]	Primary Efficacy Endpoint(% of patients with ≥75% improvement in PASI score at FT Day 84) [95% CI]	Statistical Test/ p-value	Principal Secondary Efficacy Endpoint (Subjects with OLS rating of Minimal or Clear at FT Day 84)	Statistical Test/ p-value
ACD2058g	XOMA SC	498/445		Fisher's exact		Fisher's exact
	Placebo	170/151	2.4% [0.6%, 5.9%]		2.9%	
	1.0 mg/kg/wk	162/149	38.9% [31.3%, 46.9%]	p<0.001	32.1%	P<0.001
	2.0 mg/kg/wk	166/145	26.5% [20.0%, 33.9%]	p<0.001	22.3%	P<0.001
ACD2059g	GNE or XOMA SC	597/549		Fisher's exact		Fisher's exact
	Placebo	122/111	4.9%	—	3.3%	—
	1.0 mg/kg/wk	232/211	22.4%	p<0.001	19.4%	p<0.001
	2.0 mg/kg/wk	243/227	28.4%	p<0.001	22.6%	p<0.001
	GNE SC					
	Placebo	32/25	0.0% [0–10.9]	—	0.0%	—
	1.0 mg/kg/wk	52/42	9.6% [3.2–21.0]	—	7.7%	—
	2.0 mg/kg/wk	61/60	21.3% [11.9–33.7]	—	18.0%	—
	XOMA SC					
	Placebo	90/86	6.7% [2.5–13.9]	—	4.4%	—
	1.0 mg/kg/wk	180/169	26.1% [19.9–33.2]	—	22.8%	—
	2.0 mg/kg/wk	182/167	30.8% [24.2–38.0]	—	24.2%	—
ACD2390g	GNE SC	556/520		Fisher's exact		Fisher's exact
	Placebo	187/175	4.3% [1.9%, 8.3%]		3.2%	
	1.0 mg/kg/wk	369/345	26.6% [22.1%, 31.4%]	P<0.001	25.7%	p<0.001

GNE=Genentech; NA=not available; ND=not done.
Note: All p-values represent comparison with placebo.
[a] Completed FT period or completed study, as applicable.
[b] Not referred to in protocol as principal secondary endpoint (but was the first secondary endpoint mentioned in the protocol).

Secondary endpoints:

- The proportion of subjects achieving a PGA rating of excellent or cleared at FT day 84.

	Placebo	Efalizumab 1mg/kg/wk	Efalizumab 2mg/kg/wk
Study ACD2058g	7/170 (4.1%)	63/162 (38.9%) p<0.001	50/166 (30.1%) p<0.001
Study ACD2059g	5/122 (4.1%)	52/232 (22.4%) p<0.001	69/243 (28.4%) p<0.001
Study ACD2390g	10/187 (5.3%)	122/369 (33.1%) p<0.001	Not applicable

- Mean (SD) improvement PASI thickness component at FT day 84.

	Placebo	Efalizumab 1mg/kg/wk	Efalizumab 2mg/kg/wk
Study ACD2058g	1.13 (2.22)	3.42 (2.71) p<0.001	2.73 (2.71) p<0.001
Study ACD2059g	0.91 (2.31)	3.01 (2.92) p<0.001	3.24 (3.08) p<0.001
Study ACD2390g	0.94 (1.94)	3.20 (2.82) p<0.001	Not applicable

- Mean improvement (SD) from baseline in itching scale scores during FT period. Improvement was reflected by a decrease in the 5-point itching score.

	Placebo	Efalizumab 1mg/kg/wk	Efalizumab 2mg/kg/wk
Study ACD2058g	0.5 (2.9)	2.8 (3.4) p<0.001	2.7 (3.3) p<0.001
Study ACD2059g	0.4 (1.5)	1.3 (1.6) p<0.001	1.5 (1.9) p<0.001
Study ACD2390g	0.7 (2.8)	2.8 (3.3) p<0.001	Not applicable

- Mean (SD) in percent Psoriatic BSA during FT period.

	placebo	Efalizumab 1mg/kg/wk	Efalizumab 2mg/kg/wk
Study ACD2058g	1.8 (11.6)	13.8 (15.8) p<0.001	10.0 (15.8) p<0.001
Study ACD2059g	0.3 (13.7)	9.9 (18.2) p<0.001	11.3 (18.4) p<0.001
Study ACD2390g	2.6 (9.9)	11.2 (15.1) p<0.001	Not applicable

- Mean improvement (SD) in DLQI (dermatology life quality index) overall score during FT treatment, which was reflected by a decrease in DLQI score.

	placebo	Efalizumab 1mg/kg/wk	Efalizumab 2mg/kg/wk
Study ACD2058g	2.1 (6.0)	5.3 (6.5) p<0.001	5.5 (7.2) p<0.001
Study ACD2059g	1.7 (5.1)	5.5 (6.0) p<0.001	6.0 (7.5) p<0.001
Study ACD2390g	1.6 (5.7)	5.6 (6.6) p<0.001	Not applicable

Observation period

Study ACD2058g: Of the 111 patients that entered the Observation period (OB), 100 (90.1%) discontinued early primarily because of relapse of psoriasis. The median time to protocol defined relapse during the OB period for subjects treated with efalizumab during the FT period was 60.0 days (95% CI of 57.0-66.0) for the efalizumab 1mg/kg/wk and 59.0 days (95% CI of 57.0, 82.0) for the efalizumab 2mg/kg/wk.

Retreatment period

Study ACD2058g: Eighty-two patients that received efalizumab in the FT period, entered the RT period. Of them 55 were treated with efalizumab (32 with 1mg/kg/week and 23 with 2 mg/kg/week). Of the 55 patients treated with efalizumab 13 patients (23.6%) discontinued including 12 due to non-response.

Proportion of RT-A subjects (patients who received efalizumab in the FT period and relapsed in the OB period) who achieved at least 75% PASI improvement at RT day 84:

	placebo	Efalizumab 1mg/kg/wk	Efalizumab 2mg/kg/wk
Study ACD2058g	0 (N=27)	11 (34.4%, N=32)	6 (26.1%, N=23)

All efalizumab vs. placebo p<0.001.

Based on these data of study ACD 2058g, attenuation of the response rate during retreatment compared to the response in the FT period cannot be excluded.

Extended treatment period

Study ACD2058g: Most of the patients that were considered partial responders or non responders in the FT period entered the extended treatment period. Twenty-three discontinued because they did not respond to efalizumab.

Proportion of ET-A subjects who achieved 75% PASI reduction

	Placebo	Efalizumab 1mg/kg/wk	Efalizumab 2mg/kg/wk
Study ACD2058g	4 (6.7%, N=60)	12 (21.1%, N=57)	13 (19.7. %, N=66)

All efalizumab vs. placebo p=0.018.

The results suggest that patients not responding within the first 3 months will be less likely to respond to prolonged treatment for another 3 months.

Study ACD2059g: In the extended period, patients received either efalizumab 2mg/kg/wk or efalizumab 2mg/kg/every other week or 4.0 mg/kg/wk. The majority (around 77%)of responder patients during extended treatment period maintained PASI 75 response. Attenuation of the response despite the higher dose used (2mg/kg/wk or 2mg/kg/every other week) cannot be excluded. Of the initially partial responders, 28.9% became responder in the efalizumab 2mg/kg/every other week group and 53.2% in the 2mg/kg/wk group versus 4.3% in the placebo group. Of the initially non-responders only 12.7% became responder at day 84 of the ET period with 4.0 mg/kg/wk. It should be noted that as studies ACD2058g and ACD2062g showed no added benefit for 2 mg/kg/wk in terms of efficacy vs. 1 mg/kg/wk, the latter was proposed as optimal dose for initial and long-term treatment.

Follow-up period

Study ACD2058g: Time to relapse was determined during FU period for individuals who were classified as responders at the end of the RT or ET period. The median time to protocol defined relapse during the FU ranged from 59 to 73.5 days.

Study ACD2059g: Time to relapse was determined during FU period for subjects who received efalizumab during ET period and were responders or partial responders at ET day 84. The median time was in all efalizumab groups 84 days (95% CI 77-85).

Study ACD2600g

METHODS

ACD2600g was a Phase IIIb, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Study to Evaluate the Safety of 1.0 mg/kg Subcutaneously Administered Efalizumab in Adults with Moderate to Severe Plaque Psoriasis Who Are Candidates for Systemic Therapy.

The primary objective of this study was to evaluate the safety and tolerability of a 12-week course of 1.0 mg/kg subcutaneous (SC) efalizumab relative to placebo. The secondary objectives of this study were to evaluate the efficacy of a 12-week course of 1.0 mg/kg SC efalizumab relative to placebo, as measured by the proportion of subjects who achieved a ≥75% improvement in Psoriasis Area and Severity Index (PASI), the Overall Lesion Severity (OLS) scale, the proportion of subjects who achieved a ≥50% improvement in PASI, and the Psoriatic Symptom Assessment (PSA).

The study consisted of a screening and a treatment period. All subjects started the study in the screening phase, which extended from Day –28 to Day –1. Eligible subjects continued to the treatment phase from Day 0 through Day 84. On Day 0, subjects were randomized in a 2:1 ratio to receive 12 weeks of 1.0 mg/kg SC efalizumab or placebo (initial conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 1.0 mg/kg efalizumab). Randomization was stratified within each study center by subjects' Day 0 PASI score (≤16.0, ≥16.1) and their prior treatment for psoriasis (naive to systemic treatment vs. prior systemic treatment).

At the conclusion of the 12-week treatment period, subjects who completed treatment with study drug (efalizumab or placebo) through Day 84 were given the option of receiving efalizumab in the open-label extension, Study ACD2601g. Subjects who discontinued early from this study transferred into Study ACD2601g for 12 weeks of follow-up observation.

Study Participants
Adults with plaque psoriasis covering ≥10% of body surface area (BSA) and a PASI score of ≥12.0 at screening who were candidates for systemic psoriasis therapy were randomized into the study. A subject was considered a candidate for systemic therapy if assessed by a clinician as requiring systemic therapy (e.g., psoralen with ultraviolet light [PUVA], cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine, 6-MP, etanercept) to control psoriasis, whether or not that subject had a history of receiving systemic therapy.
Criteria for exclusion included:
- History of severe allergic or anaphylactic reactions to humanized monoclonal antibodiesHistory of or ongoing infection
- HIV
- Pregnancy or lactation

Sample size
The sample size for this study was based primarily on safety considerations.

RESULTS
Participant flow and Baseline data
Overall, the two treatment groups were comparable with regard to demographic and baseline characteristics, except that the proportion of female subjects was higher in the placebo group than in the efalizumab group. The most commonly used prior systemic therapies were methotrexate (28.4%), systemic retinoids (13.4%), other unspecified systemic therapies (12.8%), systemic corticosteroids (10.3%), and cyclosporine (8.7%). Prior phototherapy was also common, including UVB (47.5%), systemic PUVA (23.0%), and topical PUVA (4.5%).
Compliance: A total of 474 subjects (69.1%) received all 12 doses of study drug.

Efficacy outcomes and estimation
In adult subjects with moderate to severe plaque psoriasis, treatment with 1.0 mg/kg/wk efalizumab for 12 weeks resulted in a statistically significant improvement compared with treatment with placebo in measures of efficacy, as defined by the principal secondary efficacy endpoint (24% versus 3%; p<0.001 vs. placebo).

PASI Response by Percent Improvement from Baseline

Percent Improvement from Baseline at Day 84	Placebo (n=236)	Efalizumab (n=450)
≥90%	0	29 (6.4%)
≥75% to <90%	7 (3.0%)	77 (17.1%)
≥50% to <75%	26 (11.0%)	128 (28.4%)
≥25% to <50%	40 (16.9%)	78 (17.3%)
≥0% to <25%	74 (31.4%)	77 (17.1%)
≥ –25% to <0%	64 (27.1%)	24 (5.3%)
≥ –50% to < –25%	11 (4.7%)	14 (3.1%)
< –50%	3 (1.3%)	9 (2.0%)
Missing a	11 (4.7%)	14 (3.1%)

A Subjects who discontinued from the study early and did not complete the Day 84 PASI assessment.

The subgroup analyses were generally consistent with the results for the randomized population as a whole.

PASI Responders by Subsets of Randomized Subjects

Subject Subset	Placebo (n=236)	Efalizumab (n=450)
Prior systemic therapy		
Yes, n	174	328
Responders, n	5 (2.9%)	81 (24.7%)
95% CI	0.9%, 6.6%	20.1%, 29.7%
No, n	62	122
Responders, n	2 (3.2%)	25 (20.5%)
95% CI	0.4%, 11.2%	13.7%, 28.7%

Statistical significant differences ($p<0.001$) in favour of efalizumab over placebo were also shown on OLS scale, patient-reported outcomes on the PSA (frequency and severity) and itching components of PSA (frequency and severity).

Study IMP24011

Study IMP24011 is a randomised multicentre phase III study consisting of a 12-week double-blind, placebo-controlled 'first treatment' (FT) period, an observation (OB) period and an open-label re-treatment (RT) period. Efalizumab was given at 1mg/kg subcutaneously once per week. FT was followed by up to 24 weeks of observation for responders (patients showing ≥75% improvement from baseline in PASI). Non-responders, partial responders and responders experiencing relapse could receive 12 weeks of open-label re-treatment, followed by 8 weeks of follow-up.

A Protocol Amendment modified the study in order to prospectively assess the safety and efficacy of efalizumab in both the total study population of patients with moderate to severe plaque psoriasis (the 'moderate to severe' population) and the subgroup of 'high need' patients, defined as patients for whom at least 2 currently available systemic therapies were unsuitable because of lack of efficacy, intolerance or contraindication. This amendment increased the planned sample size and modified study entry criteria in order to enrol sufficient numbers of 'high need' patients to permit analysis.

At the end of the observation period for PASI75 responders, or if relapse or clinical need for re-treatment is noted during the observation period, patients would enter a 12-week open-label re-treatment (RT) period. (Relapse is defined as loss of 50% or more of the improvement from baseline in PASI score observed at Week 12.) During the RT period, they would receive efalizumab 1 mg/kg subcutaneously once a week.

Only results from the first treatment (FT) were available at the time of the CHMP assessment.

METHODS

Study Participants

Patients with moderate to severe psoriasis were included. Prior and concomitant therapy was as in study ACD2600g.

Objectives

The primary objective of the study was to evaluate the safety and efficacy of efalizumab 1 mg/kg given subcutaneously once a week for 12 weeks compared to placebo. Secondary objectives were to evaluate the safety and efficacy of efalizumab during the observation and re-treatment periods.

Outcomes/endpoints
The primary efficacy endpoint was the proportion of patients showing ≥75% improvement from baseline in PASI score (PASI 75% response) after the initial 12 weeks of treatment. The primary efficacy analysis population was the Intent-to-Treat (ITT) population. Secondary endpoints similar to study ACD2600g.

Sample size
It was originally planned to enrol at least 330 patients. The above-mentioned amendment increased the planned sample size to at least 690 patients.

Randomisation
Patients meeting the study's entry criteria were randomised in a 2:1 ratio to receive efalizumab 1 mg/kg (after initial conditioning dose of 0.7 mg/kg) or placebo subcutaneously once a week for 12 weeks (the 'first treatment' or FT period). Randomisation was stratified by Psoriasis Area and Severity Index (PASI) score (≤16.0 or ≥16.1) and previous use of systemic treatment for psoriasis (yes or no) and country.

Statistical methods
The estimation of power for efficacy assumed a PASI-75 response rate of 20% in efalizumab group versus a placebo response rate of 7.5%.

RESULTS
The study was still ongoing at the time of the CHMP assessment: the present results include data from all patients up to Study Day 84.

Recruitment/Baseline data
Trial IMP24011 included 793 patients (264 were randomised to placebo and 529 were randomised to efalizumab).
As part of the 793 patients, IMP24011 included a prospectively defined cohort of 526 moderate to severe plaque psoriasis patients who met the definition for unsuitability of existing systemic therapies based on patient's history of therapy (see above-mentioned protocol amendment). These patients had a contraindication or were resistant (i.e. lack of efficacy or not controlled) or intolerant to at least two systemic therapies (such as psoralen-ultraviolet light therapy or PUVA, cyclosporin, corticosteroids, methotrexate, oral retinoids, mycophenolate mofetil (MMF), thioguanine, hydroxyurea, sirolimus, azathioprine, 6-mercaptopurine or etanercept).
The most frequently unusable medications in the define cohort were methotrexate (70.2%) > PUVA (55.9%) > retinoids (48.9%) > cyclosporine (35.7%). Main reason for the drug not to be used being resistance to therapy for methotrexate (45.6%), PUVA (35.9%) and retinoids (31.0%), and, intolerance for cyclosporine (19.2%).
Compared to the population of patients included in other psoriasis trials, this group of patients had a more severe disease as judged by the high baseline PASI score (mean: 24.4), psoriasis body surface area (38.2%), the higher frequency of arthritis associated to psoriasis (24%) and the high level of previous use of systemic therapies, with 98.7% of the patients having used 1 or more therapy, 93.0% having used 2 or more and 41.1% having used at least three systemic therapies.

Outcomes and estimation

Primary Analysis

PASI 75% Response at Day 84 in the ITT Population is provided in the table below.

Parameter	Statistics	Placebo (N=264)		Efalizumab 1.0 mg/kg/wk (N=529)	
PASI75	**N**	264		529	
	Responder	11	(4.2%)	166	(31.4%)
	Partial responder and non-responder	253	(95.8%)	363	(68.6%)
	Treatment Effect (OR*) vs Placebo	10.51			
	95% Confidence Intervals	5.59 -19.79			
	P-Value	<0.0001			

* Stratified logistic regression was used to estimate the log odds ratio for efalizumab versus placebo for PASI 75% response at 12 weeks. The logistic regression model included the randomisation factors (baseline PASI score, prior treatment for psoriasis and geographic region) as additional covariates. 'High need' status was used as a stratification variable.

Primary analysis in high need patients

In the subgroup of 'high need' patients (n= 526), PASI75 was achieved by 29.5% of the patients (placebo: 2.7%, p<0.0001). Mean PASI change from baseline was 11.8 (placebo: 2.1) and mean percent change from baseline was 46.1% (placebo: 7.6%, p<0.001).

Secondary endpoints

Other main results from IMP24011 at week 12 of treatment are presented in the table below, differentiating "high need" patients and other subjects.

Parameter	Subjects resistant or intolerant or contraindicated for systemic therapy (n = 526)		Other subjects+ (n= 267)	
	Placebo	Efalizumab	Placebo	Efalizumab
PASI75	2.7	29.5	7.5	34.8
PASI50	12.0	52.0	20.0	56.7
Mean PASI change from baseline	2.1	11.8	3.5	11.2
Mean % PASI change from Baseline	7.6	46.1	12.1	52.6
OLS (minimal or clear) %	2.7	21.3	5.0	34.8
DLQI mean change from baseline	2.3	5.4	2.5	6.2
PGA, excellent or cleared (%)	2.7	25.7	7.5	29.9
Mean % BSA improvement	-0.6	12.8	2.9	13.4
Mean PSA frequency improvement	2.1	5.8	1.9	5.6
Mean PSA severity improvement	1.9	6.3	1.9	6.2
Mean PGPA improvement	0.4	2.8	0.5	2.7

+: other subjects are those who did not met the criteria of being resistant or intolerant or having contraindication to at least two systemic therapies

PASI response to treatment was also analysed by baseline PASI category (see table below).

IMP24011.33. PASI Response to Treatment at Day 84 by Baseline PASI Category: ITT Population – All

Baseline PASI category	Statistics	Placebo (N=264)		Efalizumab 1.0 mg/kg/wk (N=529)	
<= 16.0	**Responder**	2	(2.9%)	45	(33.8 %)
	Partial responder and non-responder	68	(97.1 %)	88	(66.2 %)
	95% CI for response rate	0.3 %	9.9%	25.9 %	42.5%
16.1 - 30.0	**Responder**	8	(5.6%)	88	(31.5 %)
	Partial responder and non-responder	135	(94.4 %)	191	(68.5 %)
	95% CI for response rate	2.4 %	10.7%	26.1 %	37.3%
> 30.0	**Responder**	1	(2.0%)	33	(28.2 %)
	Partial responder and non-responder	50	(98.0 %)	84	(71.8 %)
	95% CI for response rate	0.0 %	10.4%	20.3 %	37.3%

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

In the pivotal clinical trials, inclusion has not been restricted solely to patients having received systemic treatment, which makes the studied population heterogeneous. Efficacy results in patients who were prior systemic psoriasis therapy naïve versus those patients who were pre-treated with such agents suggested that the response in these groups is similar.

PASI 75 responder by treatment by systemic therapy history, pooled data*

History of systemic Therapy	**Responder** (PASI) 75	**Placebo**	**Efalizumab** 1 mg/kg/wk	**Efalizumab** 2 mg/kg/wk
All		(N = 715)	(N=1213)	(N=409)
	Yes	25 (3.5%)	320 (26.4%)	114 (27.9%)
	No	690 (96.5%)	893 (73.6%)	295 (72.1%)
No		(N=225)	(N=353)	(N=164)
	Yes	8 (3.6%)	95 (26.9%)	40 (24.4%)
	No	217 (96.4%)	258 (73.1%)	124 (75.6%)
Yes		(N=490)	(N=860)	(N=245)
	Yes	17 (3.5%)	225 (26.2%)	74 (30.2%)
	No	473 (96.5%)	635 (73.8%)	171 (69.8%)

* Studies ACD2058g, ACD2059g, ACD2390g and ACD2600g.

- Supportive studies

Study **ACD2343g** is an ongoing phase III open-label evaluating 12 weeks of subcutaneously efalizumab and up to 132 additional weeks of continued therapy.
The long-term trial ACD2243g included 339 subjects in a 12-week induction treatment period. Those who achieved at least partial response (PASI50 or more) or OLS of cleared, minimal or mild were allowed to continue therapy for four consecutive periods of 12 weeks each, followed by another series of consecutive 12-week periods for a second year. The trial is still in progress with a third year of treatment being introduced.

The latest update of the database accounted more than 200 patients followed for one year, 171 patients treated up to 96 weeks, 158 patients up to 108 weeks (i.e. two years), 140 patients for up to 120 weeks and 75 patients up to 132 weeks.

PASI75 response after 12-week induction was achieved in 140/339 (41.3%, ITT analysis) vs. 150/339 after 24 weeks and vs 122/339 (36%, ITT analysis) at the end of the two-year period (EMT4 or 108 weeks) with an overall withdrawal rate of ≤10%. These results should be interpreted with caution because of the open nature of the study.

Withdrawal rate and main efficacy and safety results from the long-term trial ACD2243g for up to 108 weeks

Analysis	FT	MT1	MT2	MT3	MT4	EMT1	EMT2	EMT3	EMT4
Withdrawal (all)									
n	49	21	22	19	22	8	12	12	13
%	14.5	7.2	8.2	7.7	9.6	4.0	6.2	6.6	7.6
PASI75 n	140	150	157	153	147	135	131	124	122
ITT n	339	339	339	339	339	339	339	339	339
PASI75 (%)	41.3	44.2	46.3	45.1	43.4	39.8	38.6	36.6	36.0
MT-ITT n	339	290	290	290	290	290	290	290	290
PASI75 (%)	41.3	51.7	54.1	52.8	50.7	46.6	45.2	42.8	42.1
As-Treated n	339	290	269	247	228	202	194	182	170
PASI75 (%)	41.3	51.7	58.4	61.9	64.5	66.8	67.5	68.1	71.8

FT: first 12-week induction period. MT and EMT: maintenance therapy and extended maintenance therapy 12-week periods.

Open label study ACD2391g included patients from study ACD2390g that received 12 weeks initial treatment with efalizumab. In ACD2391g, subjects received additionally 12 weeks extended treatment with 1 mg/kg/wk efalizumab. 161/368 patients (43.8%) were responders after 24 weeks compared to 98/369 (26.6%) responders after the first 12 weeks of efalizumab treatment. Among the non-PASI50 responders from the first 12 weeks course on therapy, 18.9% achieved at least PASI 75. Out of the 98 responders of the FT period, 80.6% remained responders in the extended treatment period.

Study ACD2062g: Phase III open label trial for subjects who had previously completed a Phase I or II trial, or study ACD2058g, and studied the safety and tolerability of retreatment with efalizumab.

- Discussion on clinical efficacy

There were concerns regarding the clinical comparability of the Genentech and Xoma products (see clinical pharmacokinetics section and quality section). In the pivotal clinical study ACD2059g (in which both formulations were used) the efficacy results in the Genentech groups appeared to be lower and there was an apparent dose response effect with the Genentech product (9.6% of the Genentech 1 mg/kg/wk group in Study 2059g (n= 52) had a 75% PASI improvement vs. 21.3% of the 2.0 mg/kg /wk treatment group). Altogether, the enriched efficacy and safety data for the Genentech formulation allow a benefit-risk assessment of the to-be-marketed Genentech product but does not allow definitive conclusions as to the clinical comparability of the Xoma and Genentech formulations.
In response to the CHMP objections for the indication "*Treatment of adult patients with moderate to severe plaque psoriasis eligible for systemic therapy or phototherapy"*, the company provided new results of the ongoing IMP24011 study and revised the propsed indication as follows: *"Treatment of adult patients with moderate to severe chronic plaque psoriasis eligible for systemic therapy or phototherapy, whose severity of disease justifies systemic therapies and who do not adequately respond, or have a contraindication, or are intolerant to other systemic therapies".*
The company has provided 5 pivotal Phase III clinical studies in patients with moderate to severe plaque psoriasis, with efalizumab administered subcutaneously. The latest trial (IMP24011) was ongoing but the 12 weeks treatment primary results have been provided. These studies have evaluated efficacy of efalizumab primarily as monotherapy versus placebo and there is no data regarding efficacy of efalizumab versus other available systemic therapies.

Efalizumab is statistically significantly superior to placebo. For PASI 75 the absolute difference between the response to efalizumab and placebo is of deltas ranging between 17.7 and 36.5. In the most recent data on study IMP24011 for PASI 75 the absolute difference between the response to

efaluzimab and placebo was approx. 27% in the total population. In the so called "high need" group (aiming to support the new proposed indication) the results were similar (approx. 27%).
The "high need" group has been defined by the applicant as the group of patients for whom there was unsuitability of existing systemic therapies based on patient's history of therapy i.e. these patients had a contraindication or were resistant (lack of efficacy or not controlled) or intolerant to at least two systemic therapies. IMP24011 Protocol criteria for patients who are not controlled by, contraindicated to, or intolerant to two or more systemic therapies were lacking accuracy; to be judged from the patients histories of psoriasis treatments. Nevertheless, patients included under this "high need" group were shown to have a higher severity of psoriasis compared to other subjects in efalizumab trials and they also had been more pre-treated with existing therapies. As a consequence, the short-term efficacy shown versus placebo in this population is considered clinically relevant. Nevertheless, taking into account safety data and in order to better define the target population for clinical practice, it was decided to word the therapeutic indication as follows: *"Treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant of other systemic therapies including cyclosporin, methotrexate and PUVA."* Patients who *"failed to respond to"* being defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the 3 major systemic therapies as available.
Based on data on retreatment period in Study ACD2058g and on extended treatment period in study ACD2059g, attenuation of the response to efalizumab could not be excluded. Nevertheless, in Trial ACD2243g, which allowed continued therapy in a cohort of patients who achieved at least partial response after the first 12-week treatment period, PASI75 response after the first 12-week treatment had been achieved in 41% patients vs. 44% after 24 weeks and 36% at the end of the two-year period, with an overall withdrawal rate of ≤10%. These results should be interpreted with caution because of the open nature of the study. These data come from the broad population initially studied while efficacy data after 12 weeks was not available in the restricted population yet. In the broad population, a very low response rate was also observed after extended (>12 weeks) treatment of patients who did not respond in the first 12 weeks, in open label trials. As a consequence, in order to limit the exposure (see clinical safety; lack of long-term safety data, risk of psoriasis exacerbation or recurrence), it was decided that the duration of therapy should be 12 weeks and therapy may be continued only in patients who responded to treatment (PGA good or better).

Clinical safety

- Patient exposure

A total of 3,014 subjects with moderate-to severe psoriasis have been treated with efalizumab at different doses during the clinical development programme (cut-off 08 October 2003). A total of 1,730 subjects were treated with 1 mg/kg/wk efalizumab manufactured by Genentech and of which 1,395 subjects were treated for at least 12 weeks, 433 subjects were treated for at least 24 weeks, and 125 subjects for at least 84 weeks. A safety update on longer experience with the product especially from trial ACD2243g was later provided and safety results from study IMP24011 became available.

- Adverse events

Adverse events were experienced by the majority of patients. The most frequent symptomatic adverse drug reactions (ADRs) observed during Raptiva therapy were mild to moderate dose-related acute flu-like symptoms including headache, fever, chills, nausea and myalgia. In large placebo-controlled clinical studies, these reactions were observed in approximately 41% of Raptiva-treated patients and 24% in placebo-treated patients over 12 weeks of treatment.
The table below provides the adverse events that occurred in ≥3% of Patients Treated with Efalizumab 1.0 mg/kg/wk in the FT Period of the first four pivotal studies (ACD2058g, ACD2059g, ACD2390g, and ACD2600g), distinguishing the efalizumab formulations.

Adverse Events that Occurred in ≥3% of Patients Treated with Efalizumab 1.0 mg/kg/wk in the FT Period*

COSTART Body System Preferred Term	**Placebo** (n=455)	**Genentech Efalizumab** (n=930)	**Placebo** (n=260)	**XOMA Efalizumab** (n=690)
Body as a whole				
Headache	86 (18.9%)	294 (31.6%)	73 (28.1%)	248 (35.9%)
Infection	76 (16.7%)	134 (14.4%)	34 (13.1%)	91 (13.2%)
Chills	19 (4.2%)	112 (12.0%)	13 (5.0%)	95 (13.8%)
Pain	20 (4.4%)	82 (8.80%)	18 (6.9%)	85 (12.3%)
Back pain	8 (1.8%)	33 (3.5%)	6 (2.3%)	42 (6.1%)
Fever	9 (2.0%)	55 (5.9%)	15 (5.8%)	71 (10.3%)
Flu syndrome	20 (4.4%)	76 (8.2%)	9 (3.5%)	26 (3.8%)
Asthenia	16 (3.5%)	54 (5.8%)	21 (8.1%)	65 (9.4%)
Accidental injury	32 (7.0%)	47 (5.1%)	13 (5.0%)	48 (7.0%)
Digestive				
Nausea	25 (5.5%)	92 (9.9%)	26 (10.0%)	92 (13.3%)
Diarrea	28 (6.29%)	50 (5.4%)	20 (7.7%)	52 (7.5%)
Musculoskeletal				
Myalgia	22 (4.8%)	84 (9.0%)	13 (5.0%)	50 (7.2%)
Arthralgia	10 (2.2%)	31 (3.3%)	9 (3.5%)	35 (5.1%)
Respiratory				
Pharyngitis	29 (6.4%)	72 (7.7%)	18 (6.9%)	47 (6.8%)
Rhinitis	26 (5.7%)	59 (6.3%)	20 (7.7%)	39 (5.7%)
Cough increased	20 (4.42%)	40 (4.3%)	11 (4.2%)	25 (3.6%)
Sinusitis	28 (6.2%)	48 (5.2%)	6 (2.3%)	29 (4.2%)
Skin/appendages				
Herpes simplex	10 (2.2%)	37 (4.0%)	14 (5.4%)	37 (5.4%)
Acne	3 (0.7%)	33 (3.5%)	1 (0.4%)	23 (3.3%)
Pruritus	26 (5.7%)	59 (6.3%)	14 (5.4%)	30 (4.3%)

* Data pooled from ACD2058g, ACD2059g, ACD2390g, and ACD2600g

The appplicant has also submitted safety data following 12 weeks treatment of 529 patients treated with efalizumab and 264 patients with placebo in study IMP24011. The table below summarises adverse events types by treatment and by patient groups (N, %, 95% confidence intervals).

	"high need"		**"Non-high need"**	
	Placebo N=184	**Efalizumab N=342**	**Placebo N=80**	**Efalizumab N=187**
All AE	112 (60.9, 53-68)	253 (74.0, 69-79)	45 (56.3, 45-67)	130 (69.5, 62-76)
Infections	41 (**22.3**, 16-29)	88 (**25.7**, 21-31)	6 (**7.5**, 3-16)	38 (**20.3**, 15-27)
Arthritis-related	30 (16.3, 11-22)	66 (19.3, 15-24)	6 (7.5, 3-16)	21 (11.2, 7-17)
Psoriasis-related	28 (15.2, 10-21)	44 (12.9, 10-17)	8 (10.0, 4-19)	15 (8.0, 5-13)
Gastrointest.dis.	18 (9.8, 6-15)	60 (17.5, 14-22)	6 (7.5, 3-16)	18 (9.6, 6-15)
Respiratory dis.	14 (7.6, 4-12)	37 (10.8, 8-15)	7 (8.8, 4-17)	14 (7.5, 4-12)

Acute AE	38 (20.7, 15-27)	140 (40.9, 36-46)	21 (26.3, 17-37)	72 (38.5, 31-46)
Severe AE	17 (9.2, 5-14)	36 (10.5, 7-14)	2 (2.5, 0-9)	19 (10.2, 6-15)
AE leading to withdrawal	5 (2.7, 1-6)	19 (5.6, 3-9)	2 (2.5, 0-9)	11 (5.9, 3-10)
SAE	7 (3.8, 2-8)	20 (5.8, 4-9)	2 (2.5%)	9 (4.8, 2-9)

- Serious adverse event/deaths/other significant events

Serious adverse events were infrequent and there was no consistent pattern to the events suggestive of a relationship to efalizumab.

Infections
During the first 12-week treatment period, the percentage of subjects with at least one infection-related adverse event was comparable between efalizumab- and placebo-treated subjects (28.6% vs 26.3%). The observed incidence of infections requiring hospitalization among efalizumab subjects was 1.61 per 100 pt-yr, this incidence was estimated as 1.08 per 100 pt-yr in the placebo group. There was no clear evidence of an increased frequency of cases of herpes virus infections in the efalizumab-treated groups when compared to placebo. No cases of tuberculosis, toxoplasmosis, histoplasmosis or other opportunistic infections have been observed.

In the target population studied in study IMP24011, the infection rate in Raptiva-treated patients was approximately 25.7% versus 22.3% in placebo-treated patients.
Malignancies
Thirty malignancies under efalizumab were observed for 1,780 patient-years of exposure, yielding an incidence of 1.68 case per 100 patient-years, whereas 3 cancers were observed with placebo for 185 patient-years of exposure yielding an incidence of 1.62 cases per 100 patient-years. The number of cases of lymphoproliferative disorders reported for efalizumab-treated subjects was consistent with that expected in the psoriasis population. An observed increased frequency of non-melanomatous skin cancers (NMSC) in both efalizumab and placebo groups is likely to be linked to an ascertainment bias. The number of cases of solid malignancies in efalizumab-treated subjects was consistent with that expected in subjects with psoriasis and in the general US population.
Recurrence of psoriasis, erythrodermic and pustular forms of psoriasis
Recurrence of psoriasis occurred in 16% of patients after discontinuation of efalizumab and in 13% of patients under placebo. Recurrences were more frequent in patients who were non-responders.
Among 3,291 patients having received efalizumab, 29 cases of erythroderma (0.9%) and 10 cases of pustular psoriasis (0.3%) were observed during treatment or after discontinuation of treatment with efalizumab. Four cases of erythroderma were observed in 979 patients receiving placebo (0.4%). Overall, 22/39 (56%) cases occurred during treatment with efalizumab, whereas 17/39 (44%) occurred after discontinuation. The majority of these cases occurred in nonresponders.
Deafness
In the pooled results of 12 week clinical trials, the event deafness including audiometric changes was reported at a slightly higher rate in the efalizumab treatment groups (1.0% efalizumab 1mg/kg/wk, 3.7% efalizumab 2mg/kg/wk) compared to placebo group (0.6%).

See also "Discussion on clinical safety" for significant events.

- Laboratory findings

There were transient increases in circulating lymphocyte counts, and less often neutrophil or eosinophil counts, coincident with efalizumab administration and resolving after discontinuation. Between 40 and 50% of patients developed sustained asymptomatic lymphocytosis during Raptiva therapy. All values were between 2.5 fold and 3.5 fold the ULN (Upper Limit of Normal). These increases were also observed in nonclinical models and attributed to demargination and release of cells from lymph nodes.

In the combined safety database of 3291 Raptiva-treated patients, there were nine occurrences (0.3%) of thrombocytopenia with less than 52,000 cells per µl reported. Four of these patients had clinical signs of thrombocytopenia. Based on available platelet count measurements, the onset of platelet decline was between 8 and 12 weeks after the first dose of Raptiva in 5 patients, but occurred later in the other patients. In one patient, thrombocytopenia occurred 3 weeks after treatment discontinuation. The platelet count nadirs occurred between 12 and 72 weeks after the first dose of Raptiva. Therefore, platelet counts are recommended upon initiating and periodically while receiving Raptiva treatment.
The only abnormalities observed in chemistry parameters were small elevations in alkaline phosphatase and SGPT/ALT values, which did not lead to discontinuation of study treatment. Many of these subjects already had elevated alkaline phosphatase or SGPT/ALT levels at screening or baseline, prior to efalizumab exposure. A risk of hepatotoxicity for efalizumab, even small, might be augmented in alcohol abusers and should be monitored post-marketing.

- Anti-efalizumab antibodies.

The percentage of patients showing anti-efalizumab positive test at any time was 3.9% (n=98) among the 2,516 patients and the percentage of patients showing anti-efalizumab positivity at any time was 6.3% (n=67) among the 1,063 patients with the additional day 56 test.
The present absolute number of patients presenting anti-efalizumab antibodies remained too limited to allow definitive conclusions in terms of the effect on efficacy and safety.

- Safety related to drug-drug interactions and other interactions

There have been no formal drug interaction studies performed with Raptiva.
Use of concomitant medications for other disease such as hypertension, diabetic, depression, P-pills/sex hormonal therapy were continued during treatment with efalizumab. No specific adverse events were detected.
Concomitant topical steroids were used in two studies (n=262). The efficacy and safety of efalizumab did not appear to be modified by the use of topical steroids.
Given the mechanism of action of efalizumab, its effects on the immune system may be potentiated by systemic immunosuppressives commonly used for the treatment of psoriasis. Therefore, combination therapies with these products are not recommended.

- Discontinuation due to adverse events

Discontinuation from study were infrequent. Few subjects discontinued efalizumab for infections (<1%) or injection-related events (<0.5%).

- Post marketing experience

None was available at the time of the assessment.

- Discussion on clinical safety

Efalizumab appears to be safe and well tolerated in the provided relatively short-term studies.
There is no evidence of lymphocyte depletion or clinically significant toxicity affecting bone marrow, liver, kidney, or other organ systems. There was no appreciable increase in the incidence of serious infections or non-cutaneous malignancies in these short-term studies.
Eight types of common adverse events were observed to occur more frequently in subjects receiving efalizumab than placebo: headache, chills, pain, nausea, myalgia, fever, arthralgia, and peripheral oedema. Five of these events (chills, pain, fever, myalgia and nausea) were more common during the first 2 weeks of efalizumab therapy. Deafness is reported at a higher rate in the efalizumab treated groups than in the placebo group. Due to the slightly increased reports of deafness and dizziness in the efalizumab group compared to placebo the risk of these reversible ADEs should be mentioned in the SPC although the mechanism is still unknown.
There are yet no safety data past 12-week treatment in the ongoing study IMP24011 especially in relation to the newly claimed restricted indication.

There is no comparative safety data derived from prospective comparative studies with efalizumab versus active comparators.
The long-term safety data are limited especially with regard to the risk of infections, the risk of autoimmune disease, the potential for induction suppression of humoral and cellular immunity, and the risk of malignancies.

The risk of infections, autoimmune reactions and malignancy during efalizumab treatment seems to be low based on the available global safety data. However, the association of efalizumab with increased risk of infection may be of more immediate concern when continuous therapy is sought.
The interim results of study IMP 24011 reported a higher incidence of infections and infestations in efalizumab patients (21.0%) than in placebo patients (11.2%), however the incidence of infections in the placebo group "non-high need" appears particulary low. Most reported events in this category appeared to be minor infections and not suggestive of opportunistic infections that occur in immunocompromised patients. Also in the new study ACD 2600g two serious infections (pneumonia and sepsis) occurred in 2 efalizumab treated subjects (0.4%); both events led to discontinuation of treatment. The applicant recognised that the risk of infections is a potential issue and that this risk should be monitored closely and a new contraindication (patients with immunodeficiency) and a new warning regarding the risk of infection were incorporated in the SmPC.
Psoriasis related adverse events was the cause of discontinuation of treatment in approximately 0.5% of efalizumab recipients. Among 3,291 patients having received efalizumab, 22/39 (56%) cases of erythoderma or pustular psoriasis occurred during treatment with efalizumab, whereas 17/39 (44%) occurred after discontinuation. The majority of these cases occurred in non responders. In term of incidence of erythoderma or pustular psoriasis per 100 patient-years, there was nevertheless, no difference versus placebo. Nevertheless, the possibility of a rebound mechanism cannot be ruled out. In this framework, a study will be launched to investigate therapeutic options for subjects discontinuing efalizumab and experiencing reoccurrence of inflammatory psoriasis. Furthermore, a warning under section 4.4 of the SPC was introduced.
There were too limited data to exclude the potential for emergence of neutralising HAHA and related complications. The additional data limited data from trial ACD2243g seem to confirm the estimate of the occurrence of antibodies to efalizumab to be approx. 6%. However, the sensitivity of the assay for neutralising antibodies is limited the applicant should try to develop more sensitive assay in due time in addition to the intended post-marketing monitoring programme for ADEs in patients with antibodies to efalizumab.
In the controlled clinical trials at least one adverse event of arthritis was reported for 4 (1.8%) of 219 patients receiving placebo, 10 (2.4%) of 420 patients receiving 1.0 mg/kg/wk Genentech efalizumab and 5 (8.2%) of 61 patients receiving 2.0 mg/kg/wk efalizumab. Twelve (0.6%) of 1953 patients treated with efalizumab sc had a serious adverse event of arthritis, in most patients due to exacerbation/worsening of psoriasis arthritis. In the interim analysis of study IMP24011, adverse events of arthritis were observed slightly more often in subjects receiving efalizumab than placebo (10 of 125 subjects or 8.0% in the placebo group versus 28 of 252 subjects or 11.1% in the efalizumab group). Arthralgia, arthritis, back pain and arthrosis were the more common types of arthritis-related reports, occurring in 4.8%, 4.0%, 3.6% and 1.2% of efalizumab treated subjects, respectively. Bursitis, joint disorder, tendon disorder, bone pain, and neck pain were reported infrequently (<1%). Association of efalizumab use with increased risk of arthritis cannot be excluded at this moment and a warning has been included in the SPC.
Data on the association of efalizumab use with increased risk of actinic keratitis and associated acneiform eruptions are limited and should be monitored in post-marketing monitoring.
Based on ALT values, a slight and transient liver dysfunction can be observed with efalizumab. A mixed origin, liver and intestinal, appears to be the basis of the increase of alkaline phosphatase. A dose-response relationship is possible for these enzymatic elevations, such that the proposed dose of 1 mg/kg/wk allows maximisation of the benefit risk ratio of efalizumab. A risk of hepatotoxicity for efalizumab, even small, might be augmented in alcohol abusers and should be monitored this issue in post-marketing.

In summary, short-term safety does not raise concerns but considering that efalizumab is a selective immunosuppressive agent with limited safety data and limited non-clinical safety assessment, a Post

Marketing Surveillance Programme should be performed to further assess the following safety concerns:

- Autoimmune reactions, malignancy and the occurrence of serious opportunistic infections due to impact on immune response,
- Development of anti-efalizumab antibodies and adverse events seen in patients with anti-efalizumab-antibodies,
- Potential interactions,
- Evolution of actinic keratoses,
- The risk of hepatotoxicity in alcohol abusers,
- Risk of exacerbation of psoriasis or rebound.

To this purpose the Company committed to detect and assess these risks through a Post-Marketing Surveillance Programme, relying on specific pharmacovigilance monitoring and further studies.

In addition the Company will evaluate opportunities for better understanding the mechanism of action of efalizumab with a view to optimising the clinical use of the product.

5. Overall conclusions and benefit/risk assessment

Benefit/risk assessment

Quality

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application demonstrated consistent batch-to-batch production of Raptiva achieving a defined quality for the drug substance and the drug product. The fermentation and purification of the drug substance, Efalizumab, are adequately controlled and validated. Appropriate drug substance specifications have been set. The drug substance has been well characterised with regard to its physicochemical and biological characteristics using state-of the-art methods. The manufacturing process of the drug product has been described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications. The viral safety and the safety concerning other adventitious agents (including TSE) have been sufficiently assured.

Non-clinical pharmacology and toxicology

Efalizumab is a recombinant humanized monoclonal antibody that binds specifically to the CD11a subunit of LFA-1. By preventing LFA-1/ICAM binding, efalizumab may alleviate signs and symptoms of psoriasis.
Efalizumab does not cross-react with CD11a from species other than humans and a non-human primate. MuM17, a chimeric rat/mouse anti-mouse CD11a antibody was developed as a surrogate for efalizumab. Nevertheless, conventional non-clinical safety data with the medicinal product are limited and do not allow for a comprehensive safety assessment.
Increased counts of white blood cells, increased spleen weight, histological changes in the spleen, and decreased cellularity in lymph nodes, resulting in altered trafficking of white blood cells, were observed as well as platelet counts decrease.
Efalizumab inhibits both the humoral response to some antigens and the cell-mediated response. In mice an inhibition of the delayed type hypersensitivity (DTH) was observed. In pups of mice treated with an antibody analogue of efalizumab, a decrease in T-cell dependent immunity was observed. Pregnant women should not use Raptiva.
In a non-human primate, following treatment discontinuation, CD11a expression was increased to levels above pretreatment. Attention to the risk of a rebound effect should therefore be paid in human.
No evidence of carcinogenicity potential was seen in a 6-months study with p53 +/+ wild type mice with an antibody analogue of efalizumab.
Further reassurance of the safety of efalizumab should be obtained from long-term safety data in humans.

Efficacy

The provided 3 original pivotal clinical studies and the newly submitted additional two large controlled clinical trials (Studies ACD2600g, and IMP24011) have evaluated efficacy of efalizumab primarily as monotherapy versus placebo.
Study IMP24011 prospectively included patients (n=526) who were not controlled by, contraindicated to, or intolerant to two or more systemic therapies as judged from the patients histories of psoriasis treatment. Results showed that this group had a higher severity of psoriasis compared to other subjects in efalizumab trials and included patients for which several of the current therapies were unsuitable. In this study, the absolute difference between the response to efaluzimab and placebo was approximately 27% for the primary endpoint (PASI75) both in the total and the restricted populations.
This efficacy data, in line with results of previous studies, indicate modest efficacy (in terms of PASI 75 response rate). Nevertheless, it is clinically relevant in patients with moderate to severe chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant of other systemic therapies. Secondary endpoints were consistent with results of the primary endpoint through all phase III clinical trials.
In an early study, the median time to relapse (≥50% loss of improvement) in patients who initially responded to treatment (≥75% improvement on PASI after 12 weeks), ranged from 59 to 74 days following the last Raptiva dose. Therapy may be continued only in those patients who respond adequately to treatment. Re-treatment may be associated with lower or inadequate response to Raptiva than in the earlier treatment periods.

Safety

The overall exposure was up to 2,500 patient-years. Efalizumab appears to be safe and well tolerated. The most frequent adverse drug reactions observed were mild to moderate dose-related acute flu-like symptoms including headache, fever, chills, nausea and myalgia. Leukocytosis and lymphocytosis were also very common but lymphocyte returned to baseline after therapy. Thrombocytopenia was uncommon but platelet count monitoring is recommended.
The long-term safety data are limited especially with regard to the risk of infections, the risk of autoimmune disease, the potential for induction suppression of humoral and cellular immunity, and the risk of malignancies.
There are yet no safety data past 12-week treatment in the ongoing study IMP24011 especially in relation to the newly claimed restricted indication. The interim results of study IMP 24011 reported a higher incidence of infections and infestations in efalizumab patients (21.0%) than in placebo patients (11.2%) but were not suggestive of opportunistic infections.
Psoriasis related adverse events (3.2%), including erythoderma or pustular psoriasis were reported (mainly in non-responders) and the possibility of a rebound mechanism cannot be ruled out.
Antibodies to efalizumab occured approximatelly in 6% of patients. There were too limited data to exclude the potential for emergence of neutralising HAHA and related complications.
Association of efalizumab use with increased risk of arthritis, actinic keratitis and hepatoxicity in alcohol abusers could not be excluded.

As a consequence, the Company will perform a Post Marketing Surveillance Programme to further assess the safety of efalizumab (see discussion on clinical safety)".

Benefit/risk assessment

Taking into account above-mentioned efficacy and safety data, the CHMP consider that the benefit/risk assessment of Raptiva is positive in the *"Treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant of other systemic therapies including cyclosporin, methotrexate and PUVA."*
Patients who *"failed to respond to"* being defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the 3 major systemic therapies as available.

Due to the lack of long-term safety data and the risk of psoriasis exacerbation or recurrence, the duration of therapy should be 12 weeks and therapy may be continued only in patients who responded to treatment (PGA good or better).
In order to further assess potential risks especially of autoimmune reactions, malignancy, infections, adverse events due anti-efalizumab-antibodies and interactions, the Company will perform a Post Marketing Surveillance Programme.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Raptiva in the *Treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant of other systemic therapies including cyclosporin, methotrexate and PUVA* was favourable and therefore recommended the granting of the marketing authorisation.