Title of Trial: A multicentre, open label Phase IIIb/IV study of subcutaneously administered efalizumab 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 ciclosporin, methotrexate and PUVA

Investigational Product: Raptiva® (efalizumab - recombinant humanized monoclonal anti-CD11a antibody)

Trial No.: 25300

Study Centers: This study was conducted in 170 centres in 18 European countries: Austria (10 centres), Belgium (8 centres), Czech Republic (3 centres), Denmark (4 centres), Finland (4 centres), France (27 centres), Germany (17 centres), Greece (5 centres), Hungary (2 centres), Ireland (3 centres), Italy (35 centres), Norway (4 centres), Poland (5 centres), Portugal (7 centres), Slovakia (1 centre), Spain (19 centres), Sweden (4 centres) and the United Kingdom (12 centres).

Trial Initiation Date: 13 December 2004

Trial Completion Date: 25 January 2007

Development Phase: 3b/4

Publication (reference): None

Study Objectives:

Primary: To establish control of moderate to severe chronic plaque psoriasis with efalizumab in subjects who had failed to respond to, had a contraindication to, or were intolerant to other systemic therapies including ciclosporin, methotrexate and Psoralen + UVA phototherapy (PUVA).

Secondary:

- To evaluate the management of psoriasis events, namely rebound and exacerbation, occurring during efalizumab treatment or after its discontinuation.

  - Rebound was defined as worsening of disease in responders (i.e., subjects with Physician's Global Assessment [PGA] ratings of "Good or better" at Week 12 of the First Treatment period) as assessed by Psoriasis Area and Severity Index (PASI) score >125% of baseline or new pustular, erythrodermic, or more inflammatory psoriasis occurring within 2 months of stopping therapy.

  - Exacerbation was defined as disease worsening in non-responders (i.e., subjects with PGA ratings of "fair" or worse at FT Week 12) either during or after treatment which was more inflammatory in nature compared to baseline and occurred either within

pre-existing plaques, at previously uninvolved sites, or as new morphologies of disease.

- To identify genes or DNA polymorphisms associated with certain traits (response, adverse events) in subjects with moderate to severe psoriasis receiving treatment with efalizumab as well as potential susceptibility loci for psoriasis.

Tertiary:

- To evaluate other metrics important for the treatment of psoriasis, including health-related quality of life (QOL), pharmacoeconomics, and treatment efficacy with respect to the nails, scalp and palmoplantar areas, and

- To investigate the biological mechanisms of psoriasis events (rebound and exacerbation) in subjects discontinuing efalizumab therapy.

Methodology:

Subjects were screened for trial participation during a period of up to 14 days before the planned start of treatment (Study Day 0, defined as the day of first administration of the trial medication). Those found eligible were required to discontinue all systemic psoriasis therapies before beginning trial treatment.

Following verification of adherence to washout requirements and discontinuation of systemic psoriasis therapies, subjects entered the First Treatment (FT) period, during which they received 12 weeks of treatment with open-label efalizumab (1.0 mg/kg given once weekly by subcutaneous injection, with an initial conditioning dose of 0.7 mg/kg administered once at Week 1).

Subjects who completed the First Treatment period had various options for continuing in the trial, depending on their Physician's Global Assessment (PGA) response at FT Week 12.

- FT period responders (those with PGA ratings of "Good", "Excellent" or "Cleared" at FT Week 12) could choose to receive Continuous Treatment (CT) with efalizumab on a compassionate basis until commercial drug became available. These subjects had a final follow-up visit 8 weeks after their last FT period visit, which was considered the end of their trial participation.

- FT period non-responders (those with PGA ratings of "Fair" or worse at FT Week 12 or earlier) could enter the Transition Treatment (TT) period, during which they received 12 weeks of treatment with another medication approved for the treatment of moderate to severe psoriasis, chosen by the Investigator or treating physician based on the subject's medical and treatment history.

- Subjects who did not wish to receive any anti-psoriatic therapy – regardless of FT period response status – could enter the Observational (OB) period, which would last for up to 8 weeks. In case of disease recurrence during this period that was more

inflammatory than baseline, FT period responders would enter the Re-Treatment (RT) period, during which they would receive 12 weeks of re-treatment with open-label efalizumab, and FT period non-responders would enter the Transition Treatment period (described above).

Subjects who discontinued prematurely from the FT period were to have the assessments planned for FT Week 12 at the time of discontinuation. Those who discontinued because of worsening of disease compared to baseline or because of psoriasis-related adverse events would then enter the TT period; those who discontinued for other reasons would have a final follow-up visit 8 weeks after their last FT period visit.

Subjects who discontinued the TT or RT period prematurely were to have the assessments planned for TT/RT Week 12 at the time of early termination.

All subjects were to have a final follow-up visit, which would occur 8 weeks after the last visit of the FT, RT or TT period. Subjects of the OB period did not have a follow-up visit.

Number of Subjects (Planned and Analyzed):

Planned: 1500; Screened: 1421; Enrolled: 1266.

Diagnosis and Main Criteria for Inclusion/Exclusion:

The trial recruited adult subjects with moderate to severe plaque psoriasis who had failed to respond to, had a contraindication to, or were intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA.

Main inclusion criteria were discontinuation of systemic psoriasis therapies before Study Day 0 (SD 0, defined as the day of first administration of trial medication), discontinuation of investigational treatments and biologicals other than efalizumab at specified times before SD 0, written informed consent and (where appropriate) agreement to use adequate contraception throughout the trial and for 3 months after the last dose of trial medication. Subjects who had received previous treatment with efalizumab could enter the trial if they satisfied all eligibility criteria.

Main exclusion criteria were guttate, erythrodermic, or pustular psoriasis as sole or predominant form of psoriasis, withdrawal from previous efalizumab treatment due to lack of efficacy or adverse event, pregnancy or breast-feeding, white blood cell count $<4.0 \times 10^9$/L or $>14.0 \times 10^9$/L, history of clinically significant thrombocytopenia, bleeding disorders or a platelet count $<100 \times 10^9$ cells/L and concurrent medical conditions that in the Investigator's judgement would jeopardise the subject's safety following exposure to trial medication.

Study Treatment:

Raptiva® (efalizumab), given subcutaneously at 1.0 mg/kg once a week with an initial conditioning dose of 0.7 mg/kg.

Duration of treatment: 12 weeks (FT period); 20 weeks (FT+CT periods, i.e. 12+8); 24 weeks (FT+RT periods, i.e 12+12)**.**

Reference Therapy, Dose and Mode of Administration:

Not applicable

Criteria for Evaluation:

Efficacy Endpoints:

Primary: Physician's Global Assessment (PGA) ratings of "Good", "Excellent" or "Clear" at FT Week 12.

Secondary: Safe Psoriasis Control (a composite endpoint incorporating PASI, Dermatology Life Quality Index scores and safety outcomes) at FT Week 12, Overall Lesion Severity (OLS) rating of "Clear", "Minimal" or "Mild" at FT Week 12, OLS ratings over time, PGA ratings over time, incidence of rebound and time to rebound during the OB period (responders only), incidence of relapse and time to relapse during the OB period (responders only), incidence of exacerbation during or after treatment (non-responders only).

Tertiary: Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), Nail Psoriasis Severity Index (NAPSI), Psoriasis Scalp Severity Index (PSSI), Palmoplantar

Psoriasis Area and Severity Index (PPPASI), Medical Outcomes Study Short Form-36 (SF-36, called "regional QOL questionnaire" in the protocol) biological and histological markers of disease activity.

Safety:

Adverse events, serious adverse events and laboratory abnormalities in subjects on efalizumab therapy; testing for antibodies to efalizumab.

Other:

Pharmacogenetic outcomes (described below; identified as an optional assessment and as "secondary efficacy endpoint" in the Protocol) measured at any trial visit.

Pharmacoeconomic outcomes (Resource Utilisation Questionnaire; identified as "tertiary efficacy endpoint" in the Protocol) measured at baseline and FT Week 12.

Statistical Methods:

A sample size of 1500 subjects would give at least 95% probability that an adverse event of frequency 0.2 % would result in one case in the sample. In this trial, the actual sample size of 1266 subjects would give at least 95% probability that an adverse event of frequency 0.24%

would result in one case in the sample, or at least 92% probability that an adverse event of frequency 0.2% would result in one case in the sample.

Populations:

- For the FT period, the Intention-to-Treat (ITT) population was to include all subjects who received at least one dose of treatment and had at least one post-dose efficacy assessment (i.e. PGA or PASI) available during the FT period. The Safety population was to consist of all subjects who received at least one injection of efalizumab.
- The Continuous Treatment (CT) population was defined to include all subjects who received at least one dose of efalizumab during the CT period.
- The Transition Treatment (TT) population was defined to include all subjects who received at least one dose of transition treatment other than efalizumab (confirmed to be transition treatment by the Medical Responsible) during the TT period.
- The Observational (OB) population was defined to include all subjects who entered the OB period.
- The Re-treatment (RT) population was defined to include all subjects who received at least one dose of efalizumab during the RT period.

FT period analyses of subject disposition, baseline characteristics (including medical history and disease characteristics), concomitant treatments, compliance/exposure, efficacy and antibodies to efalizumab were performed using the ITT population; analyses of adverse events, safety laboratory outcomes and vital signs were performed using the safety population.

After the FT period, subject disposition, baseline characteristics, concomitant treatments, efficacy and safety were analysed by period for the CT, TT, OB and RT populations. Safety data from the 8-week final follow-up visits was analysed separately for subjects followed up after the TT period and for those followed up after the FT, OB or RT period.

Analyses:

Analyses for this trial were primarily descriptive in nature and no formal hypothesis testing was performed.

Exact 95% confidence intervals (CI) for proportions were obtained using PROC FREQ in SAS. PROC LIFETEST in SAS was used to generate Kaplan –Meier estimates.

No interim analysis was performed and no sub-groups were defined. However, sub-populations of the ITT population (CT, OB, RT and TT) were used for the relevant post-FT endpoints.

Efficacy:

For the primary efficacy endpoint, the primary analysis was performed using the ITT population, considering subjects with missing FT Week 12 PGA ratings to be non-responders (worst outcome imputation). Numbers and proportions of subjects achieving each rating

("Cleared", "Excellent", "Good", etc.) and with ratings of "Good or better" and "Fair to Worse" were summarised, and a 95% confidence interval (95% CI) presented for the proportion with ratings of "Good or better".

A sensitivity analysis was performed using last observation carried forward (LOCF) for missing FT Week 12 values.

For the secondary efficacy endpoints, the analysis was performed using the ITT population with the corresponding confidence interval (95% CI). Incidence of rebound and relapse and time to rebound and relapse were summarised using Kaplan-Meier estimates. No graphical representations were presented as had been initially planned.

Because the psoriasis events included in the per protocol definition of rebound ("new pustular, erythrodermic, or more inflammatory psoriasis") are not part of the MedDRA coding system, a review of reported adverse events was performed and a trial-specific interpretation of the definition was formulated in order to facilitate the programming of the rebound output. This definition did not deviate from the protocol definition; it simply selected the relevant AEs for this trial.

Exacerbation in non-responders was identified using the same adverse event terms described above for rebound; however, "aggravation of nail psoriasis" was also considered.

For the tertiary efficacy endpoints, all scores were summarised by visit within each period. For SF-36, if a subject responded to at least half of the questions in a given scale, then the sub-scale score was calculated using the mean of the responses of the non-missing questions; otherwise the scale score was to be reported as missing.

Safety:

Adverse events were coded using MedDRA (version 8.1). Summary tables included System Organ Classes (SOCs) and Preferred Terms; derived listings also included Lower Level Terms.

Reported adverse events were classified as pre-FT period, FT treatment-emergent or post-FT period events based on their onset dates and the dates of first and last FT period treatment administration.

Clinical laboratory data (haematology and biochemistry) were summarised by visit (including baseline values and changes from baseline) for each trial period. Worst CTC grading (version 3.0) for each period was also summarised.

Past and concomitant medications (ongoing at or started after Study Day 0) were summarized by ATC (Anatomic, Therapeutic, Chemical) code for each trial period, using WHO DRUG version 2006-Q1.

Vital signs were summarised by visit (including baseline values and changes from baseline) for each trial period. Proportions of subjects with measurable antibody response to efalizumab were summarised by visit for each trial period.

Others:

Pharmacogenetic analysis: DNA from subjects who provided separate informed consent was analysed for DNA polymorphisms that could influence response to treatment or adverse events as well as potential susceptibility loci for psoriasis. Analyses were performed by comparison of allele frequency of biallelic markers and single nucleotide polymorphisms (SNPs) spread throughout the human genome. Methodology used included DNA amplification, genotyping and statistical analysis. Traits were studied in two extreme groups (i.e. responders and non-responders). The Sponsor tested for significant differences in allelic frequencies across the different trial groups for each single SNP genotyped (single point analysis). The evidence of a significant difference for a marker between groups is a strong indication of association with the given trait.

Resource Utilisation Questionnaire: Based on the Resource Utilisation Questionaire, medical resource utilisation (i.e. number of visits to general practitioners, dermatologists etc.) was summarised separately for each type of health care professional. Social impact was also summarised including the number of days off work due to sickness, change in work status and change in spouse or career status.

Results:

Subject Disposition: Of the 1421 subjects screened from 13 Dec 2004 to 12 Apr 2006 for participation in this trial, 1266 subjects were found to be eligible and were enrolled and treated with efalizumab, and 155 subjects were considered screening failures. Of the 1266 enrolled subjects, 1084 completed treatment during the FT period, whereas 182 withdrew prematurely; the ITT population included 1255 subjects since 11 subjects did not provide any post-baseline efficacy assessment (i.e. PGA or PASI) during the FT period.

In the ITT population (1255 subjects), 853 subjects were responders and 402 were non-responders at FT Week 12; 171 subjects discontinued treatment prematurely during the FT period and 185 subjects had a final follow-up visit as per protocol.

Of the 853 responders, 696 entered the Continuous Treament (CT) period; however, only 688 subjects received treatment with efalizumab during this period (CT population=688 subjects).

Seventy-four (74) subjects entered the Transition Treatment (TT) period; however, only 68 received treatment during this period with other approved psoriasis therapies (TT population=68 subjects).

One hundred and fifty-six (156) subjects did not wish to continue treatment and went into the Observation Period (OB population=156 subjects). Of the 156 subjects in the OB population, 114 entered the Re-Treatment (RT) period to receive an additional 12 weeks of treatment with efalizumab; however, only 113 subjects received treatment during this period (RT population=113 subjects). None of the non-responders who entered the OB period entered the TT period subsequently.

Some of the subjects during this trial entered treatment/assessment periods that were inappropriate for their response or trial period completion status. Further details on these subjects may be found within this report.

Demographics and Baseline Characteristics: Subject age ranged from 18 to 81 years, with a median of 46 years. Eight hundred and sixty (860 or 68.5%) subjects were male and 395 (31.5%) were female. The majority of the subjects were white (1233 subjects or 98.2%), 6 subjects were black (0.5%), 10 subjects were Asian (0.8%) and 6 subjects were of other ethnic groups (0.5%). Subjects' height ranged from 146 to 198 cm, with a median of 172 cm. Body weight ranged from 45.0 to 160.7 kg, with a median of 80.0 kg, and body mass index ranged from 16.4 to 64.4 kg/m2, with a median of 26.71 kg/m^2.

The most frequently reported medical conditions at baseline were hypertension, hypercholesterolaemia, depression and diabetes mellitus.

Duration of psoriasis since diagnosis ranged from 0.7 to 66.1 years, with a median of 18.68 years. Eight (8) of the 1255 subjects (0.6%) had completed the CLEAR study (). Previous psoriasis therapies were reported for 1243 subjects (99.0%), and previous systemic therapies for1218 subjects (97.1%). Prior medications included selective immunosuppressive agents (ciclosporin, infliximab, mycophenolate mofetil, efalizumab) and topical antipsoriatic medications.

At baseline, the median PASI score was 19.55 (range: 0.7-67.2); 51.3% of subjects had baseline PASI scores <20.0.

Baseline DLQI scores ranged from 0.0 to 30.0, with a median of 10.0. Baseline SF-36 summary scores ranged from 40.0 to 792.0, with a median of 571.5; SF-36 physical scores ranged from 10.0 to 400.0, with a median of 298.0, and SF-36 mental scores ranged from 13.0 to 400.0, with a median of 268.8.

Approximately half of the subjects had "moderate" baseline OLS scores (653 subjects or 52.1%), followed by 516 or 41.2% of the subjects with "severe" and 40 or 3.2% of the subjects with "very severe" baseline OLS scores.

Efficacy Results:

Primary endpoint:

The proportion of subjects with Physician's Global Assessment (PGA) ratings of "Good or better" at Week 12 of the FT period (n=1255) was 68.0% (95% CI: 65.3-70.5%) (853 subjects). Using LOCF, the PGA response was 69.1% (95%CI: 66.4-71.6%) (867 subjects).

Secondary endpoints:

- The proportion of subjects achieving Safe Psoriasis Control (defined as satisfying all of the following: PASI"8, DLQI"6, no serious adverse events, no severe

treatment-related adverse events and no premature withdrawal) at FT Week 12 (n=1255) was 39.0% (95%CI: 36.3-41.7%) (489 subjects).

- The proportion of subjects achieving an Overall Lesion Severity (OLS) rating of "Mild" or better at FT Week 12 was 65.3% (95%CI: 62.6-67.9%) (819 subjects) with 6.1% "Clear" (77 subjects) (baseline: 44 subjects or 3.5% had OLS rating of "Mild" or better with no "Clear" subjects).
- At TT Week 12 (n=68), the proportion of subjects with PGA response of "Good or better" was 52.9% (36 subjects), with 4.4% "Clear" (3 subjects). At Week 1, the proportion of subjects with PGA response of "Good or better" was 5.9% (4 subjects) with no "Clear" subjects.
- The OLS response for "Mild" or better at TT Week 12 (n=68) was 55.9% (38 subjects) with 5.9% "Clear" (4 subjects) (baseline: 5.9% or 4 subjects had OLS of "Good or better" with no "Clear").
- The PGA response for "Good or better" at RT Week 12 (n=113) was 55.8% (63 subjects) with 2.7% "Clear" (3 subjects). By Week 8, the corresponding PGA response was 45.1% (51 subjects) with no "Clear" subjects (Week 1: 20.4% or 23 subjects had PGA rating of "Good or better").
- The OLS response for "Mild" or better at RT Week 12 (n=113) was 60.2% (68 subjects) with 5.3% "Clear" (6 subjects) (baseline: 1.8% or 2 subjects had OLS rating of "Mild" or better with no "Clear" subjects)
- Relapse (defined as loss of ≥50% of the PASI improvement achieved at the end of the initial 12 weeks of treatment with efalizumab) and rebound were evaluated during the OB period for those subjects who were classified as responders at FT Week 12.
  - 56.7% of the 127 responders analysed in the OB period (n=135) experienced relapse, with a median time to relapse of 56 days.
  - 11.0% of the 127 responders analysed in the OB period (n=135) experienced rebound. The median time to rebound was not reached, as only 11.0% of subjects experienced rebound; subjects not experiencing rebound were censored at the end of OB, i.e. after 8 weeks. The 25th percentile for time to rebound was 66.0 days.
- Exacerbation was evaluated during treatment and post-treatment periods, only for those subjects who were assessed as non-responders at FT Week 12; 52 subjects or 12.9% of the non-responders experienced at least one occurrence of exacerbation during this trial.
- In order to identify markers of efficacy of treatment with efalizumab, psoriasis-related events and disease severity at baseline, an exploratory pharmacogenetic analysis was performed. Only a few efficacy markers were identified, none of which was fully associated with the clinical outcome. All markers identified during this analysis were risk markers (i.e. no marker was 100% associated with the clinical outcome), with a relative risk of being a higher responder or a lower responder of 1.4-2.0. Nevertheless, no major conclusions can be drawn at this stage due to the exploratory and preliminary nature of these results.

Tertiary endpoints:

- The median NAPSI score at FT Week 12 was 20.0, compared to a median baseline score of 24.0. A NAPSI 75 was observed in 14.1% (95%CI: 11.7-16.7%).
- The median PSSI score at FT Week 12 was 3.0 (baseline: 16.0). A PSSI 75 response was observed in 49.3% (95%CI: 46.3-52.4%)
- The median PPPASI score at FT Week 12 was 1.20 (baseline: 4.00). A PPPASI 75 was observed in 48.6% (95%CI: 41.8-55.5%)
- PASI 75 response at FT Week 12 was observed in 35.9% (95%CI: 33.3-38.7%); PASI 50 (at least 50% improvement from baseline) response at FT Week 12 was observed in 65.5% (95%CI: 62.8-68.1%). There were no differences in baseline PASI scores among subjects who entered the FT, CT, OB, RT and TT periods; for all these groups, median PASI baseline scores ranged from 17.40 to 19.80. At Week 12, the median PASI scores for the FT, RT and TT populations were 6.00, 5.70 and 4.90 respectively. At CT Week 20, the median PASI score was 3.90.
- The median score for DLQI at FT Week 12 was 3.0, compared to a median score of 10.0 at baseline. At Week 20 of CT, the median score for DLQI was 2.0 (baseline same as in FT).
- The median summary score for SF-36 at FT Week 12 was 645.0, compared to the median baseline score of 571.5. At Week 20 of CT, the median SF-36 summary score was 658.5, compared to the median baseline score of 564.8. (N.B. higher scores represent better quality of life).

In summary, control of moderate to severe chronic plaque psoriasis was achieved for the majority of the subjects in this trial during the initial 12 weeks of treatment. Clinical outcomes continued to improve in responders during continuous treatment with efalizumab. Following discontinuation of treatment, re-treatment of responders with efalizumab appeared to be beneficial. Non-responders to efalizumab were generally controlled after transitioning to other systemic therapies. Pharmacogenetic analysis revealed potential response markers to treatment with efalizumab. No markers of psoriasis-related events (i.e., rebound, relapse, exacerbation) and severity were identified.

Safety Results:

Efalizumab showed an acceptable safety profile in this trial, which was largely consistent with that observed in previous trials.

The most frequent treatment-emergent adverse events (TEAEs) during the first 12 weeks of treatment (FT period) were headache, pyrexia, influenza-like illness and arthralgia, consistent with the syndrome of "acute adverse events" known to occur with initial efalizumab treatment.

Because of the immunomodulatory mechanism of action of efalizumab, infections were closely monitored. During the CT and RT periods, the most commonly reported TEAEs by MedDRA SOC were "Infections and infestations" (primarily minor infections such as nasopharyngitis).

The most frequent serious TEAEs and the most frequent AEs leading to treatment discontinuation were largely skin and subcutaneous tissue disorders (i.e. psoriasis,

erythrodermic psoriasis) and musculoskeletal and connective tissue disorders (i.e. arthralgia, psoriatic arthropathy), as has been previously reported.

Five malignancies, 4 during the FT period and one during the FU after the RT period, were reported during this trial (by Preferred Term: 2 squamous cell carcinomas, 2 basal cell carcinomas and one penis carcinoma). Two of these were considered serious and possibly related to trial medication. In one of the two cases of squamous cell carcinoma the subject had a previous medical history of basal and squamous cell carcinoma. No firm conclusions can be drawn about possible increase in risk of malignancy with the use of efalizumab from these few cases

One subject died of cardiopulmonary failure. A 71-year-old male received a single dose of efalizumab and was discontinued from trial medication 5 days later due to the onset of an upper respiratory infection. The subject suffered cardiopulmonary failure approximately 4 weeks after his single efalizumab dose. The event was assessed as unlikely to be related to trial medication.

Apart from expected increases in lymphocyte and total WBC counts, laboratory findings were generally unremarkable. Changes in blood chemistry parameters did not reveal any significant patterns.

A total of 1250 subjects were tested for antibodies to efalizumab at screening. Blood samples taken from 964 subjects (77.1%) at screening did not provide any results due to the use of unsuitable sample tubes. Blood samples drawn from the remaining 286 subjects (22.9%) tested negative for antibodies to efalizumab. None of the 69 evaluable subjects tested positive at RT Week 12. Similarly, only a small percentage of subjects tested positive at the end of CT (2.3% [480 evaluable subjects]). It should be noted that RT and CT blood samples were taken while subjects were still under treatement. Small yet slightly higher percentages of subjects tested positive at the end of other periods (TT: 7.1% [28 evaluable subjects], and FU: 3.6% [112 evaluable subjects]). Ten (10) subjects or 11.8% tested positive at the end of the OB period (85 evaluable subjects).

In summary, reported adverse events and laboratory abnormalities in this trial were consistent with expected findings in a population with moderate to severe chronic plaque psoriasis undergoing treatment with efalizumab. No new safety concerns were identified.

Conclusions:

This trial provides information addressing important clinical questions that arise at the end of the first 12 weeks of treatment. According to the present European label for efalizumab, only subjects who respond to treatment may continue after this point, while non-responding subjects should be discontinued. These questions therefore include appropriate management of responding subjects (continuous treatment vs. cyclic treatment) and management of nonresponding subjects following discontinuation of efalizumab (transition to alternative antipsoriatic treatment or observation).

Results from the CT period, in which 79.5% of subjects had a PGA of "Good" or better at the end of treatment, substantiate the view that continuous treatment with efalizumab maintains psoriasis control in the large majority of subjects.

To evaluate treatment options for responding subjects, it is interesting to compare CT period results with those from the RT period, in which responders who were observed without treatment for 8 weeks or until worsening were re-treated. Re-treatment with efalizumab led to a substantial proportion (55.8%) of subjects with PGA ratings of "Good" or better at the end of 12 weeks, suggesting effective control of disease recurrence in previous efalizumab responders. However, adverse events – notably musculoskeletal disorders - were reported in a higher percentage of subjects during the RT period than during the CT or OB periods.

Overall, these data show that interrupting efalizumab treatment in responding subjects leads to a loss of response, a higher incidence of psoriasis worsening compared to continuous treatment and a risk of disease rebound. Loss of response and rebound can be managed by re-treatment; however, the incidence of adverse events in general and arthritis related adverse events in particular may be higher with re-treatment compared to continuous treatment. In summary, results in FT period responders strongly support the recommendation of continuous treatment with efalizumab rather than cyclic treatment in subjects who show response to treatment at Week 12.

Rebound and relapse were evaluated in FT period responders who entered the OB period.

Among 127 subjects evaluable for rebound and relapse (i.e., FT responders who entered the OB period and had PASI scores available), 14 (11.0%) experienced rebound: this frequency is comparable to results of previous trials. Seventy-two (72) subjects (56%) relapsed, with a median time to relapse of 56.0 days.

The question of the appropriate management of non-responders is of great clinical interest. Results of this trial suggest that the optimal solution for subjects who discontinue efalizumab because of non-response may be transition to other anti-psoriatic treatments. Approximately 50% of non-responders who received transition treatment achieved PGA response. In contrast, response was observed in approximately 30% of non-responders who entered the CT period, suggesting that transition to alternative therapy is the better option for these subjects.

The trial does not provide robust data permitting comparison of transition treatment with simple observation, as few non-responders entered the OB period and use of anti-psoriatic treatments was permitted during the FU period. However, the incidence of psoriasis exacerbation in non-responders was lower during the OB, TT and FU periods than during the FT period, suggesting that discontinuation of efalizumab (or of the transition therapies examined) in these subjects is not associated with psoriasis-related adverse events.

Results of quality of life assessments (SF-36, DLQI) supported the beneficial role of treatment with efalizumab. Assessment of scalp, nail and palmoplantar disease, using the PSSI, NAPSI and PPPASI respectively, showed meaningful improvement in these difficult-to-treat areas.

One of this trial's objectives was to identify predictive markers for efficacy during the first 12 weeks of treatment. To address this objective, an exploratory pharmacogenetic analysis was performed in which a few efficacy markers were identified that were correlated with response or non-response. However, none of these markers was fully associated with the clinical outcome. Further work is needed to identify better predictors of response or non-response, and no major conclusions can be drawn at this stage. Concerning the investigation of biological mechanisms of psoriasis events after discontinuation of efalizumab, findings suggested that the cell population playing a dominant role in the pathogenesis of psoriasis could vary during the course of the disease: results of these analyses will be reported as an Addendum to this Clinical Trial Report.

Overall, the safety profile of efalizumab in this trial was consistent with the experience gathered in previous trials and from post-marketing surveillance. No new safety concerns were identified.

The most frequent treatment-emergent adverse events (TEAEs) during the FT period were consistent with the syndrome of "acute adverse events" known to occur with initial efalizumab treatment; the most frequent TEAEs in subsequent periods were minor infections such as nasopharyngitis. The most frequent serious TEAEs and the most frequent AEs leading to treatment discontinuation were skin and subcutaneous tissue disorders (i.e., psoriasis, erythrodermic psoriasis) and musculoskeletal and connective tissue disorders (i.e., arthralgia, psoriatic arthropathy), as has been previously reported. One subject died due to cardiopulmonary failure during the FU period; this event was assessed as unlikely to be related to trial medication. Because of efalizumab's immunomodulatory mechanism of action, infections and malignancies were closely monitored. Most reported infections were minor. Five malignancies were reported, two of which were considered possibly related to trial medication; however, no inference can be drawn from these few cases about possible increase in risk. Apart from expected increases in lymphocyte and total WBC counts, laboratory findings were unremarkable.

The majority of subjects in this trial, for whom other systemic therapies were unsuitable due to lack of efficacy, intolerance or contraindication, benefited from efalizumab's favourable efficacy and safety profiles. The clinical outcomes from this trial provide information that may be useful in development of a treatment algorithm and management principles. Subjects who completed the FT period and continued efalizumab therapy during the CT period appeared to show the greatest benefit from treatment. Results from other trial periods suggest that responding subjects can discontinue treatment if necessary, but should be closely observed after discontinuation for signs of relapse (observed in more than 50% of cases) or rebound (observed in 11%). Psoriasis-related events such as rebound and exacerbation can be successfully managed with either efalizumab re-treatment or transition to other anti-psoriatic treatments. Subjects not responding to efalizumab may experience exacerbation of psoriasis either during therapy or upon its discontinuation; therefore, it is crucial that these subjects be monitored carefully and transitioned immediately to other anti-psoriatic therapies to achieve control of their disease.