Title of Trial: A multicentre, open label and subsequent randomised, double blind, placebo controlled phase III study to assess the safety and efficacy of maintenance and extended therapy with subcutaneously administered onercept of subjects with moderate to severe plaque psoriasis who have either responded or partially responded to an initial 12-week induction treatment with onercept

Investigational Product: Onercept (r-hTBP-1)

Trial No.: 24981

Study Centers: This study was conducted in 94 clinical centres in 22 countries.

Trial Initiation Date: August 2004

Trial Completion Date: June 2005

Development Phase: Phase 3

Publication (reference): None

Study Objectives:

Primary Objective:

- To assess the safety and efficacy of maintenance therapy with onercept 150 mg TIW compared to matching placebo in subjects having achieved a PASI 75 response (improvement of ≥ 75% from baseline in PASI score) at the end of an initial 12-week induction treatment with onercept 150 mg TIW.

Secondary Objectives:

- To assess the safety and efficacy of extended therapy with onercept 150 mg TIW compared to matching placebo in subjects who only achieved a partial response (PASI 50 to 74) after an initial 12-week induction course with onercept 150 mg TIW.

Methodology:

Multicentre, randomised, double blind, placebo-controlled phase III study, with three treatment periods followed by a 4-week safety follow-up (FU) period for each subject.
Open Label First treatment (OLFT) period: Eligible subjects with moderate to severe plaque psoriasis were to receive onercept 150 mg for 12 weeks. Study visits were at Weeks 2, 4, 8 and 12. Depending on their PASI response at the Week 12 visit, the subjects were to enter **a) Maintenance Treatment (MT), b) Extended Treatment (ET),** or **c)** they were to be withdrawn from the study. **a) MT period:** Subjects who, at the end of the 12-week OLFT period, achieved at least 75% improvement in their PASI compared to baseline (responders) were to be randomised in a ratio of 1:1 to receive either onercept 150 mg or matching placebo

TIW for 40 weeks or until relapse (defined as loss of at least 50% of the improvement achieved between baseline and the end of the 12-week OLFT period). Randomisation was stratified by PASI improvement at Week 12 of the OLFT period (75% -<90% vs. ≥ 90%), prior treatment for psoriasis (naïve to systemic treatment vs. prior systemic treatment) and geographical region. Study visits were every 4 weeks. **b) ET period**: subjects who, at the end of the 12-week OLFT period, achieved at least 50% but less than 75% improvement in their PASI compared to baseline (partial responders) were to be randomised in a ratio of 1:1 to receive either onercept 150 mg or matching placebo TIW for 12 weeks. Randomisation was stratified by prior treatment for psoriasis and geographical region. Study visits were every 4 weeks. At the end of the 12-week ET period subjects were to enter the **open label extended treatment (OLET) period** until they had completed 52 weeks of therapy in total. During OLET, study visits were every 4 weeks. In addition, subjects who relapsed at any time during the MT period, were to enter the OLET. **c)** Subjects who had an improvement in their PASI of less than 50% at the end of the 12-week OLFT period compared with baseline (non-responders) were to be withdrawn from the study. Upon completion of a subject's final treatment period, or upon withdrawal from treatment, subjects entered a 4-week safety FU period.

Number of Subjects (Planned and Analyzed):

Planned 900; enrolled: 991

Diagnosis and Main Criteria for Inclusion/Exclusion:

Eligible subjects were outpatients aged at least 18 years, with plaque psoriasis for at least 12 months and covering at least 10% of total body surface area, PASI score ≥ 12.0 and sPGA score ≥ 3 at screening, and were candidates for phototherapy or systemic therapy. Subjects were required to provide written informed consent before undergoing any study procedures that were not part of their normal medical care; female subjects could be neither pregnant nor breastfeeding and had to lack childbearing potential, either by being post-menopausal or surgically sterilised or by using adequate contraception for the duration of the study.

Subjects were excluded if they had participated in another study or used specified treatments (e.g. systemic psoriasis treatments, >1 non-steroidal anti-inflammatory drug, systemic corticosteroids, cyclosporin, methotrexate, oral retinoids, fumaric acid esters, or phototherapy) within specified periods before study entry, had histories of cancer, active tuberculosis, or other major concomitant illness, had to be immunised or vaccinated during the study period, or had clinically significant psoriasis flares at screening.

Study Treatment:

Onercept (recombinant human tumour necrosis factor binding protein-1 [r-hTBP-1]) 150 mg injected by the subcutaneous (SC) route TIW.

Duration of Treatment: Up to 52 weeks: Open-label treatment (OLFT) for 12 weeks followed by a double-blind randomised period, either as a) MT for 40 weeks or until relapse or b) ET

for 12 weeks, and then open-label treatment (OLET) following relapse from MT or completion of ET, until Week 52.

Reference Therapy, Dose and Mode of Administration: Placebo injected by the SC route TIW during the MT and ET periods.

Criteria for Evaluation:

Efficacy: Efficacy evaluations included PASI, sPGA, PsA-GA, quality of life and self-evaluation questionnaires (SF-36, Itching Scale and Dermatology Life Quality Index [DLQI]). The study's primary efficacy endpoint was to be the time to relapse for subjects achieving PASI 75 at Week 12 of the OLFT period, defined as the loss of at least 50% of the improvement in PASI achieved at Week 12 (OLFT period) with respect to baseline (Study Day 1). The planned secondary endpoints included the time to loss of PASI 50 response during the MT period for PASI 75 responders at Week 12 (OLFT) period.

Safety: Safety was evaluated through symptom-directed physical examinations (including vital sign measurements), clinical laboratory assessments (including haematology, chemistries and urinalysis) and evaluation of reported adverse events.

Statistical Methods:

Populations:

As a result of the decision to terminate the study, it was decided that only the safety population would be analysed. For each study period, the safety population consisted of all randomised subjects who received at least one injection of study medication and had post-baseline safety data from the period under analysis; subjects were analysed as treated.

Analyses:

Following the early termination of the study, it was decided to focus on analysis of safety data. Efficacy analyses were limited to summaries of the improvement in PASI score for each treatment period and of the number of subjects with a worsening of PASI score (defined as an increase of more than 25% from baseline) for the OLFT period only. No statistical hypothesis testing was performed. The following baseline data are summarised in tables: demography, psoriasis disease history, history of psoriasis therapy, and baseline psoriasis characteristics. In addition, subject disposition, reasons for withdrawal, AEs (including serious adverse events [SAEs]), concomitant medications, vital signs, haematology, biochemistry and urinalysis, compliance and exposure to study treatment are summarised. Treatment-emergent adverse events were coded using MedDRA (version 7.0) and summarised by study period. Special attention was given to SAEs, injection site reactions, infections, hypersensitivity reactions, neoplasms, myelosuppression, demyelinating disorders and heart failure. Safety laboratory values, vital signs and changes from baseline in these parameters were summarised by study period; for safety laboratory values, percentages of subjects considered 'outliers' were summarised, and for systolic blood pressure, diastolic blood pressure and pulse, percentages of subjects with • 20% change from baseline were summarised. In addition to summary tables,

demographic data, exposure and compliance, all AEs and those leading to premature discontinuation, SAEs, and deaths are presented in individual data listings.

Results:

Subject Disposition:

OLET period: A total of 991 subjects (all of whom were included in the safety population) were enrolled in the study; 820 subjects (82.7%) completed the OLFT period, 110 (11.1%) withdrew prematurely from OLFT, and 61 subjects (6.2%) were ongoing in OLFT at the time of termination. Of the 110 subjects who were withdrawn from OLFT prior to study termination, 57 (51.8%) were withdrawn due to AEs, 32 (29.1%) due to lack of efficacy, 4 (3.6%) due to protocol deviations and 17 (15.5%) for 'other reasons'.

MT period: Following completion of the OLFT period, 154 subjects (all of whom were included in the safety population) were randomised to the MT period (75 to placebo and 79 to onercept); 134 subjects (87.0%) were ongoing in the period at study termination, 18 subjects (11.7%) relapsed (9 on each treatment) and 2 subjects (1.3%), both on onercept, were withdrawn prior to study termination due to AEs; no subject had completed the MT period by the time the study was terminated.

ET period: Following the completion of the OLFT period, 308 subjects were randomised to the ET period, 154 to each treatment group. Of the 301 subjects included in the safety population (150 on placebo and 151 on onercept), 229 subjects (76.1%) were ongoing in the ET period at the time of study termination (112 on placebo and 117 on onercept), 45 subjects (15.0%) completed the period (21 on placebo and 24 on onercept) and 27 subjects (9.0%) were withdrawn from it prior to study termination. Of the 27 subjects who were withdrawn, 10 subjects (37.0%) were withdrawn due to lack of efficacy (7 on placebo and 3 on onercept), 3 subjects (11.1%) due to AEs (1 on placebo and 2 on onercept), 1 subject (3.7%) on onercept due to a protocol violation and 13 subjects (48.1%) for 'other reasons' (9 on placebo and 4 on onercept).

OLET period: 63 subjects (59 of whom were included in the safety population) either started the MT period and subsequently relapsed (18 subjects) or completed the 12-week ET period (45 subjects) and continued to the OLET period. All of these 63 subjects were ongoing in the OLET period at study termination.

FU period: Of the 991 subjects enrolled into the study, 889 subjects (89.7%) underwent the 4-week safety FU.

Demographics and Baseline Characteristics:

At enrolment into OLFT (baseline), the median age of the subjects was 44 years and some 70% of them were males. At randomisation to the MT and ET periods, demographic characteristics were well balanced between the treatment groups.

Efficacy Results (Safety Population): Some improvements in PASI were observed in subjects on onercept. Nevertheless, the results were below expectations.

Safety Results (Safety Population):

Overall, the safety profile of onercept was consistent with prior experience. A substantial proportion of subjects (e.g. 62.2% of patients in the OLFT period) treated with the drug experienced injection site reactions (ISRs), particularly erythema and pruritus. Four of the ISRs were reported as serious. Further, ISRs contributed to the withdrawal of 31 subjects from the study due to AEs. Headache was also commonly reported (11.3% of subjects in the OLFT period), as were upper respiratory tract infections (about 19% of subjects in the OLFT period). Infections were common during the study and, except for a higher frequency of upper respiratory tract infections on onercept during the ET period, the rates of infections between the onercept and placebo groups were rather similar and do not suggest increased risk of infection associated with onercept treatment. There were no reports of demyelinating disorders, but events suggestive of hypersensitivity, neoplasms, myelosuppression and heart failure were reported during the study. Yet, the numbers of events were small – especially during the placebo-controlled periods – and hence no conclusion about potential increase in risk with treatment may be drawn.

Laboratory abnormalities, in terms of both changes in median over time and outlier values, consisted primarily of elevations in eosinophils and lymphocytes and decreases in platelets and neutrophils. A consistent median increase of eosinophils and decrease in the neutrophil and platelet counts were seen over time during the OLFT period. Further, during the randomised ET period, subjects who continued treatment with onercept showed continued decreases in neutrophils and platelets compared to baseline, exceeding those continuing in the placebo group. Little change was observed during the study in summary statistics for biochemistry values, including liver enzymes.

Between February and March 2005, one subject from this study and another from a different study presented with an overall clinical picture of severe sepsis. Based upon a review of these cases, other safety data, and blinded efficacy data, the study's independent Data Safety Monitoring Board (DSMB) recommended stopping the three ongoing phase III onercept trials due to the apparently unfavourable risk-benefit balance. This recommendation was endorsed by Serono's Safety and Ethics Committee, and the three phase III clinical studies were discontinued on 6 Apr 2005. Subsequent to study discontinuation, a second subject from this study presented with a clinical picture suggestive of sepsis. No infectious aetiology was identified in any of the cases.

Conclusions:

In summary, the drug showed many of the risks associated with other anti-TNF agents, but with less benefit than anticipated. The formal analysis of study data thus supports the company's decision to discontinue development of onercept in the treatment of psoriasis due to its unsatisfactory benefit-risk ratio in this condition.