Title of Trial: A multicentre, randomised, double blind, placebo controlled phase III study of subcutaneously administered onercept in the initial treatment and continued treatment after extended therapy in subjects with moderate to severe plaque psoriasis

Investigational Product: Onercept (r-hTBP-1)

Trial No.: 24978

Study Centers: This study was conducted in 33 clinical centres in 9 countries (Bulgaria, Chile, Estonia, Latvia, Lithuania, Mexico, Romania, Russia and Ukraine).

Trial Initiation Date: 28 September 2004

Trial Completion Date: 31 May 2005

Development Phase: Phase 3

Publication (reference): None

Study Objectives:

Primary Objective:

- First Treatment (FT) period: To assess the safety and efficacy of an initial 12-week treatment course with onercept 150mg three times a week (TIW) for the induction of remission in subjects with moderate to severe plaque psoriasis, compared to matching placebo.

Secondary Objectives:

- Open Label (OL) period: To assess the safety of continuous onercept therapy for 28 weeks in subjects having received an initial 12-week treatment course with onercept 150 mg TIW or placebo.
- Randomised Withdrawal (RW) period: To assess the safety and efficacy of withdrawal of therapy after 28-40 weeks of continuous treatment by comparing onercept 150 mg TIW with matching placebo during a 12-week placebo-controlled randomised withdrawal period.

Methodology:

Multi-centre, randomised, double-blind, placebo-controlled study, with three treatment periods (FT, OL, and RW) and a 4-week safety follow-up (FU) period.

FT period: eligible subjects with moderate to severe plaque psoriasis were randomised in a 1:1 ratio to receive either onercept 150 mg or matching placebo for 12 weeks. Randomisation was stratified by Psoriasis Area and Severity Index (PASI; ≤20, >20), by prior systemic treatment for psoriasis within the last 5 years (yes / no) and by region (Russia, the rest of Europe and

Latin America). Visits were at Weeks 1, 2, 4, 8 and 12, and major efficacy assessments included PASI, Nail Psoriasis Severity Index (NAPSI), Static Physician's Global Assessments (sPGA), dynamic PGA, and Psoriatic Arthritis Global Assessment (PsA-GA).

OL treatment period: all subjects who completed the FT period entered the open -label (OL) onercept 150 mg treatment period for 28 weeks. Visits at every 4 weeks included assessments of PASI and dynamic PGA.

RW period: at the end of the OL treatment period, subjects who achieved PASI 75 at Week 12 and 40 were to be re-randomised in a 1:1 ratio to receive either onercept 150 mg or matching placebo for 12 weeks. (Subjects who had not achieved PASI 75 were to start the 4-week FU period). Visits every 4 weeks were to include assessments of PASI, NAPSI, sPGA, dynamic PGA, and PsA-GA. Adverse events (AEs) were assessed throughout the study. Note: due to the early discontinuation of the study, no subjects entered the RW period.

FU period: All subjects were to have a safety FU visit 4 weeks after completion of the RW period or premature discontinuation.

Number of Subjects (Planned and Analyzed):

Planned: at least 460 subjects; enrolled: 511 subjects.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Eligible subjects were outpatients aged 18-75 years with plaque psoriasis for at least 12 months and covering at least 10% of total body surface area, with PASI score ≥ 12.0 and sPGA ≥ 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. Up to 52 weeks: 12 weeks of double-blind placebo-controlled FT followed by 28-week OL treatment and 12-week double-blind placebo-controlled RW treatment. Note: due to the early discontinuation of the study, the median time on OL treatment was only 27 days (range 1–99) and no subjects entered the RW period. Placebo injected by the SC route TIW.

Criteria for Evaluation:

Efficacy: Efficacy evaluations included PASI, Dynamic PGA, sPGA, NAPSI, PsA-GA, quality of life and self-evaluation questionnaires (SF-36, Itching scale and Dermatology Life Quality Index [DLQI]), and skin biopsy. The primary efficacy endpoint was to be the proportion of subjects with at least a 75% improvement in PASI score between baseline (Study Day 1) and Week 12 of the FT period; the secondary efficacy endpoints included the proportion of subjects attaining a PGA rating of Cleared or Almost Cleared at Week 12 of the FT period.

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

Statistical Methods:

Populations:

As a result of the decision to terminate the study, it was decided to analyse only the safety population. The Safety Population consisted of all randomised subjects who had received at least one injection of study medication and had post-baseline safety data in the period under analysis (FT or OL). Due to the early termination of the study, no subjects entered the RW period.

Analyses:

Following the early termination of the study, no statistical analyses were performed. Efficacy analyses were limited to 2 summary tables: the improvements in PASI score at Week 12/Early Termination of the FT period and at Week 28/Early Termination of the OL period, and the numbers of subjects with worsening of PASI score (defined as PASI >125% of baseline) during the FT period and OL period, both summarised by FT treatment groups. The following data are summarised in tables: baseline data (demography, psoriasis disease history, history of psoriasis therapy, and baseline psoriasis characteristics), subject disposition and reasons for withdrawal, AEs (including serious adverse events [SAEs]), concomitant medications, vital signs, haematology, biochemistry and urinalysis, and compliance and exposure to study treatment. Treatment-emergent AEs were coded using Medical Dictionary for Regulatory activities (version 7.0) and summarised by study period. Special attention was given to SAEs, injection site reactions (ISRs), 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 and SAEs were presented in individual data listings.

Results:

Subject Disposition: A total of 511 subjects were randomised to FT; 256 subjects were randomised to placebo (safety population; 255 subjects) and 255 subjects to onercept (safety population; 254 subjects). Of the 509 subjects in the safety population, 18 (3.5%) withdrew prematurely: 3 were withdrawn due to AEs, 1 was lost to follow-up, 1 had a protocol deviation and 13 withdrew for other reasons. A total of 490 subjects entered the OL period; 249 had been on FT placebo (safety population; 248) and 241on FT onercept (safety population; 239). At the time of study termination, 99.4% of the subjects in the safety population were ongoing in the study and 3 subjects had been withdrawn from the OL period; 2 were withdrawn due to AEs and 1 due to lack of efficacy. No subjects entered the RW period. All the 509 subjects in the FT safety population entered the safety FU period.

Demographics and Baseline Characteristics: Demographic and other baseline characteristics were well balanced between the subjects assigned to placebo and onercept. The median age of study subjects was 45 years, and 70.5% of the subjects were males.

Efficacy Results (Safety Population): The efficacy data from Week 12 showed that the subjects on onercept had their PASI scores improved more than the subjects on placebo. Nevertheless, the improvement on onercept was below expectations.

Safety Results (Safety Population):

During the FT period: AEs were reported in 44.7% of the subjects on placebo and in 61.0% of the subjects on onercept. The most common AEs were injection site erythema, injection site pain, injection site pruritus and headache. The events related to injection site reactions were more common in subjects on onercept than in subjects on placebo; headache occurred in roughly the same proportion of subjects in both the onercept (8.7%) and placebo (7.8%) groups. SAEs were reported in 1 subject (0.4%) in each treatment group; the SAE on onercept (acute left-sided pneumonia of the lower lobe) was evaluated by the Investigator as possibly related to study treatment. More subjects on onercept (n = 133; 52.4%) than onplacebo (n = 52; 20.4%) reported pre-specified treatment-emergent AEs: ISRs were most common and were reported in 42.5% of the subjects on onercept and in 7.8% of subjects on placebo; infections were reported in 15.0% of the subjects on onercept and in 11.4% of the subjects on placebo; hypersensitivity was reported in 3 of the subjects (1.2%) in onercept and in 5 of the subjects (2.0%) on placebo; cardiac failure was reported in 1 subject (0.4%) on placebo; bone marrow suppression was reported in 3 subjects (1.2%) on onercept and 1 subject (0.4%) on placebo; and neoplasm (skin papilloma) was reported in 1 subject (0.4%) in each of the treatment groups.

During the OL period: AEs were reported in 26.2% of the FT placebo subjects and in 12.1% of the FT onercept subjects. SAEs were reported in 3 subjects (0.6%) that had been on FT placebo; in the opinion of the Investigator, one of the events (erythema at the injection site) was probably related to the study treatment and the two other ones (meningioma and tachycardia) were possibly related to the study treatment. More subjects on FT placebo (n = 55; 22.2%) than on FT onercept (n = 14; 5.9%) reported pre-specified treatment-emergent

AEs during OL; ISRs we most common and reported in 20.2% (50 subjects) of the subjects on FT placebo and in 0.8% (2 subjects) of subjects on FT onercept; infections were reported in 6 (2.4%) of the subjects on FT placebo and in 9 (3.8%) of the subjects on FT onercept; hypersensitivity was reported in 1 subject (0.4%) who was on placebo during the FT; cardiac failure and bone marrow suppression were each reported in 1 subject (0.4%) on FT onercept; and neoplasm was reported in 1 subject (0.4%) in each of the FT groups (meningioma on FT placebo and skin papilloma on FT onercept).

During the FU period: A total of 4.7% of the subjects in the safety population experienced at least one AE. SAEs were reported in 3 subjects (0.6%) in the safety population; in the opinion of the Investigator, one of the events (drug-reactive hepatitis) was probably related to the study treatment.

There were no deaths in the study. During the study, 10 subjects discontinued treatment because of AE. Of the AEs that led to discontinuation, 5 were assessed as probably related to study treatment (injection site reactions in 4 subjects and leukopenia in 1 subject); 3 were reported as possibly related (worsening of psoriasis, tachycardia and meningioma; each reported in 1 subject) and 2 were assessed as unlikely to be related to the study treatment (an SAE of fracture of the lower limb and rib, and a case of hepatitis B infection). The incidences of laboratory (haematology and biochemistry) and vital sign outliers appeared similar between the treatment groups over time.

Conclusions:

This study was one of Serono's three phase III clinical studies to assess the efficacy and safety of onercept in moderate to severe plaque psoriasis. Two patients participating in other, concurrent onercept studies presented with an overall picture suggestive of sepsis. A meeting of the DSMB in April 2005 reviewed these cases, other accumulated safety data and blinded efficacy data. The DMSB recommended stopping all three ongoing phase III onercept studies in light of an apparent unfavourable risk-benefit balance. This recommendation was endorsed by Serono Safety and Ethics Committee and the three phase III clinical studies were discontinued on 6 Apr 2005. Due to the discontinuation of this study, the analyses of efficacy were reduced to summaries of the improvements in PASI score at Week 12/ET visit of the FT period and at ET visit of the OL period, and of the numbers of subjects with worsening of PASI score (defined as PASI >125% of baseline) during FT and OL. The efficacy data from Week 12 show that the subjects on onercept had their PASI scores improved more than the subjects on placebo. Nevertheless, the improvement on onercept was below expectations.

No cases of patients presenting with a clinical picture of sepsis were reported in this study. In most subjects, the safety profile of onercept was consistent with prior experience. A significant proportion of subjects treated with the drug experienced injection site reactions, particularlyerythema and pruritus. In some cases these reactions were severe and serious. Headache was also commonly reported in onercept-treated subjects, although the incidence was roughly the same as in subjects treated with placebo. Onercept treated subjects are more likely to experience mild to moderate and transient elevations in liver enzymes and eosinophil counts.

Further, decreased platelet counts may be associated with onercept treatment. There was no clear evidence of increased risk of infection associated with onercept treatment. Similarly, there was little or no evidence of myelosuppression, demyelinating disorders, drug hypersensitivity or heart failure. 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.