Synopsis (C0743T12 ACCEPT)

Name of Sponsor/Company: Centocor Research & Development, Inc.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: Ustekinumab		
Name of Active Ingredient: Ustekinumab		
Protocol: C0743T12	**EudraCT No.:** 2006-003444-30	
Title of the study: A Phase 3, Multicenter, Randomized Study Comparing Ustekinumab and Etanercept for the Treatment of Moderate to Severe Plaque Psoriasis		
Principal/Coordinating Investigator: Professor Christopher Griffiths, The Dermatology Centre, The University of Manchester, Hope Hospital, Salford, Manchester, UK		
Study Centers: 67 investigative sites: 2 sites in Austria, 4 sites in Belgium, 18 sites in Canada, 2 sites in Denmark, 3 sites in Finland, 6 sites in Germany, 3 sites in the Netherlands, 4 sites in the UK, and 25 sites in the US.		
Publication (reference): None		
Studied Period: 26 Mar 2007/15 Jan 2009	**Phase of Development:** 3	
Objectives: The primary objectives of this study were to compare the efficacy of ustekinumab to etanercept and evaluate the safety of ustekinumab and etanercept. The secondary objective was to evaluate the efficacy and safety of retreatment with ustekinumab.		
Methodology: This was a Phase 3 multicenter, randomized, active-controlled, parallel, 3-arm study of SC injections of ustekinumab 45 mg at Weeks 0 and 4, ustekinumab 90 mg at Weeks 0 and 4, and etanercept 50 mg twice weekly through Week 12 in subjects with moderate to severe plaque psoriasis. Subjects were randomized in a 3:5:5 ratio. No subjects were to receive injections with etanercept after Week 12 by design. Treatment after Week 12 was dependent on PGA response at Week 12 and initial treatment assignment.		
Number of Subjects (Planned and Analyzed): 850 planned in a 3:5:5 ratio; 903 were randomized; all randomized subjects were treated and included in efficacy and safety analyses. Among the 556 subjects who were randomized to and treated with ustekinumab, 551 had samples available for pharmacokinetics analysis and 542 were analyzed for antibodies to ustekinumab. Two hundred and eighty-seven subjects from the etanercept group who were treated with ustekinumab 90 mg after Week 12 were also evaluated for antibodies to ustekinumab.		
Diagnosis and Main Criteria for Inclusion: Subjects eligible for this study were men and women 18 years of age or older with moderate to severe plaque psoriasis who had a Psoriasis Area and Severity Index (PASI) ≥ 12, Physician's Global Assessment (PGA) ≥ 3, and had at least 10% of their body surface area (BSA) involved. Subjects must have been naïve to ustekinumab and etanercept and must have had an inadequate response, been intolerant, or had a contraindication to at least 1 conventional antipsoriatic systemic therapy (methotrexate [MTX], cyclosporine, or psoralen plus ultraviolet A light [PUVA]) and must have been considered by the investigator to be an appropriate candidate for etanercept according to the Enbrel® product label approved by their country.		

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Test Product, Dose and Mode of Administration, Batch Number:
Etanercept Europe: Etanercept was supplied as lyophilized product containing 25 mg per vial. All subjects in Europe had to administer 2 injections of reconstituted etanercept in order to receive the 50 mg dose. At the Week 0, Week 4, and Week 8 visits, subjects were given 4 kits, with each kit containing enough etanercept for 1 week of treatment. One lot of lyophilized etanercept 25 mg (24366) was used in Europe during the study.
Etanercept North America: Etanercept was supplied as a 50 mg liquid formulation in a prefilled syringe. Subjects in Canada and the US had to administer 1 injection in order to receive the 50 mg dose. At the Week 0, Week 4, and Week 8 visits, subjects were given 2 kits of etanercept, with each kit containing enough etanercept for 2 weeks of treatment. Each kit contained 4 prefilled syringes with 50 mg of etanercept. Six lots of liquid etanercept 50 mg (P073240, P074069, P082141, P084218, P099846, and P099848) were used during the study in Canada and the US.
Ustekinumab: Ustekinumab (45 mg and 90 mg) was supplied as a sterile liquid for SC injection at a volume of 0.5 mL or 1.0 mL in a single-use prefilled syringe. Three lots of ustekinumab 45 mg (903393, 905450, and 908382) and 2 lots of ustekinumab 90 mg (903394 and 905451) were used during the study. Ustekinumab and matching placebo were supplied to the study sites in kits, each of which contained 1 prefilled syringe of ustekinumab (either 0.5 mL or 1.0 mL) and 1 prefilled syringe of matching placebo (either 0.5 mL or 1.0 mL). Each kit had a unique 5-digit kit number, but was not labeled as either 45 mg or 90 mg ustekinumab in order to maintain the blind.

Duration of Treatment: For subjects randomized to etanercept, the first to last administration of etanercept was 12 weeks of treatment and subsequent administrations of ustekinumab 90 mg were dependent on PGA response at Week 12 and was up to 4 weeks of treatment with ustekinumab. For subjects randomized to ustekinumab, the first to last administration of ustekinumab was up to 44 weeks of treatment. Initial administrations occurred at Weeks 0 and 4 while subsequent administrations were dependent on PGA response at Week 12 and initial treatment assignment.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Matching Placebo for Ustekinumab: Matching placebo for ustekinumab was supplied as a sterile liquid for SC injection at a volume of 0.5 mL or 1.0 mL in single-use prefilled syringes. Two lots each of matching placebo for ustekinumab 45 mg (903396 and 906065) and matching placebo for ustekinumab 90 mg (903395 and 906064) were used during the study. Ustekinumab and matching placebo were supplied to the study sites in kits, each of which contained 1 prefilled syringe of ustekinumab (either 0.5 mL or 1.0 mL) and 1 prefilled syringe of matching placebo (either 0.5 mL or 1.0 mL).

Criteria for Evaluation: All randomized subjects were summarized in the description of the study population. All randomized subjects were included in the primary efficacy analysis and were analyzed according to the randomized treatment group. Secondary efficacy analyses were based on all randomized subjects or on the subset of subjects with available outcome measurements according to their randomized group. Safety evaluations were based on subjects who received at least 1 administration of study agent; subjects were analyzed according to the actual treatment received.

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Pharmacokinetics/Pharmacodynamics: Serum samples collected at Weeks 0, 4, 12, 16, 24, 32, 44, and 64, at Week R0, and at any termination visit were used to determine serum ustekinumab concentrations. However, for this report, data were only summarized from samples collected through Week 16 and at Weeks R0 and R24 for PGA responders at Week 12. Per protocol, subjects who were PGA responders could receive additional doses of ustekinumab at any time from Week 16 through Week 64, therefore, serum concentration data collected at Weeks 24, 32, 44, and 64 could not be categorized into a single treatment group for PK evaluation. Serum concentration data were summarized through Week 40 for PGA nonresponders at Week 12. Serum samples collected prior to study agent administration at selected visits through Week 64 were used to determine antibodies to ustekinumab.

Efficacy: The primary and the first 3 major secondary efficacy endpoints were described in the Week 12 CSR (refer to the 12-Week C0743T12 CSR for further details on these results). This report summarizes results of the fourth major secondary endpoint (the difference between the PASI score achieved at Week 12 and that achieved at Week R12 with a corresponding 2-sided 95% confidence interval (CI) will be presented by treatment group for subjects randomized to ustekinumab and retreated upon recurrence of psoriasis) as well as other efficacy evaluations.

Safety: Safety was assessed by: 1) AEs and SAEs that occurred at and between each of the evaluation visits; 2) TB evaluation; 3) routine laboratory analyses and changes over time (hematology and chemistry); and 4) ECG results. Safety data through Week 64 are presented herein for AEs, SAEs, and laboratory analyses. ECG results were presented in the Week 12 CSR (refer to the 12-Week C0743T12 CSR for further details on these results).

Statistical Methods: Descriptive statistics, such as counts and percentages for categorical measurements, mean, SD, median, interquartile (IQ) range, minimum and maximum for continuous measurements were used to summarize most data. The comparison of 2 timepoints of a continuous parameter was evaluated by constructing a 2-sided Wald 95% CI on the difference of the 2 timepoints. Time to event data were analyzed using life-table methods. Subjects who had not experienced specified events by the last visit were right-censored. For all efficacy analyses, subjects were analyzed according to the treatment to which they were randomized, regardless of the treatment they actually received.

SUMMARY – CONCLUSIONS

Study Population Results:
The demographic characteristics of the overall study population were discussed in the 12-Week CSR. For both PASI scores and the proportions of subjects by PGA score at retreatment, treatment groups remained well-balanced. Upon retreatment, the burden of disease was generally lower than that observed at baseline. PASI scores were lower than that observed at baseline, with median scores ranging from 7.00 to 8.40, and a higher proportion of subjects had moderate PGA scores (from 93.1% to 94.7%), and lower proportions of subjects had PGA scores of marked (from 4.9% to 6.1%) or severe (from 0.4% to 1.3%).

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Pharmacokinetic/Pharmacodynamic Results:

- For subjects randomized to ustekinumab who were PGA responders at Week 12, median serum ustekinumab concentrations at Week 4, Week 12, and Week 16 were higher in the ustekinumab 90 mg group than those in the ustekinumab 45 mg group, with the difference between the 2 groups showing dose-proportionality.
- At the time of recurrences of psoriasis, the majority of subjects treated with either ustekinumab 45 mg or 90 mg exhibited serum ustekinumab concentrations below the LLOQ (< 0.17 μg/mL).
- Subjects randomized to ustekinumab who were PGA responders exhibited higher median serum concentrations of ustekinumab than those who were PGA nonresponders.
- For all subjects treated with ustekinumab, the overall incidence of antibodies to ustekinumab through Week 64 was low with 32 (3.8%) subjects developing antibodies to ustekinumab. Antibody responses to ustekinumab were predominantly low titer.
- For those subjects who crossed over to ustekinumab 90 mg from etanercept treatment, the incidence of antibodies to ustekinumab through Week 64 was low, with 7 (2.4%) subjects developing antibodies to ustekinumab.

Efficacy Results:

- After treatment interruption at Week 12, the median duration of PGA response was 14.4 weeks in the ustekinumab 45 mg group, 18.1 weeks in the ustekinumab 90 mg group, and 7.3 weeks in the etanercept group.
- As measured by PASI scores, retreatment with ustekinumab 45 mg and 90 mg provided a treatment benefit similar to that observed following the initial treatment.
- The majority of subjects in the ustekinumab 45 mg (79.6%) and 90 mg (86.3%) groups regained PGA response at Week R12 after reinitiating treatment.
- Among ustekinumab subjects who were Week 12 PGA nonresponders, approximately 37% of subjects converted to PGA responders at Week R28 with 1 additional dose at Week 16.
- Among etanercept PGA responders, 85.5% reachieved a PGA of cleared, minimal, or mild 12 weeks after crossing over to ustekinumab 90 mg.
- Among etanercept PGA nonresponders, 70.2% achieved a PGA of cleared, minimal, or mild 12 weeks after crossing over to ustekinumab 90 mg, and 40.4% achieved a PGA of cleared or minimal.

Safety Results:

Ustekinumab therapy was generally well tolerated through Week 64.

Adverse Events

- Through Week 64, the proportions of subjects experiencing at least 1 AE were similar in the ustekinumab treatment groups: 87.1% and 89.0% in the 45 mg and 90 mg groups, respectively. The most frequently reported AEs in both ustekinumab groups were nasopharyngitis and upper respiratory tract infection.
- The overall pattern of AEs in the ustekinumab groups was generally comparable with that reported in the 24-Week CSR; there were no consistent dose effects and the rates of AEs did not increase disproportionately with the increased follow-up.

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- Among subjects in the etanercept group, the proportion of subjects with at least 1 AE was greater prior to crossover (79.3%) than following crossover to ustekinumab 90 mg (64.7%). Notable differences prior to crossover versus after crossover to 90 mg were for headache (11.8% and 3.1%, respectively), injection site erythema (15.3% and 0.7%, respectively), injection site hematoma (7.2% and 0, respectively), and injection site swelling (7.2% and 0, respectively).

Serious Adverse Events

- Through Week 64, the proportions of subjects experiencing 1 or more SAEs were comparable between the 45 mg and 90 mg groups (8.1% in the 45 mg group, and 7.2% in the 90 mg group).
  - The most common SAEs observed through Week 64 occurred in the Gastrointestinal disorders system-organ class (1.4% and 1.7% in the 45 mg and 90 mg groups, respectively) and the Infections and infestations system-organ class (0.5% and 2.3% in the 45 mg and 90 mg groups, respectively).
- No impact of crossover from etanercept to ustekinumab on SAEs was apparent through Week 64.

Safety of Retreatment

Analyses of AEs and SAEs did not reveal concerning safety signals in subjects who interrupt ustekinumab treatment and re-initiate treatment following recurrence of psoriasis.

Deaths

Through Week 64, 3 deaths were reported: gunshot wound (45 mg), multisystem organ failure in a subject who was HIV positive (90 mg), and motor vehicle accident (etanercept → 90 mg).

Infections

- Generally comparable proportions of subjects in the ustekinumab 45 mg group (63.6%) and 90 mg group (66.0%) had 1 or more infections through Week 64. No apparent difference in the pattern of overall infections or infections requiring oral or parenteral antimicrobial treatment was observed.
- No impact of crossover from etanercept to ustekinumab on infections was apparent through Week 64.
- Through Week 64, serious infections occurred in 2.9% of subjects in the 90 mg group and 1.0% in the 45 mg group. Among subjects who crossed over from etanercept to ustekinumab 90 mg, serious infections were observed in 0.3% of subjects.
- There were no cases of TB or serious opportunistic infections.

Cardiovascular Events

- Through Week 64, comparable proportions of subjects in the ustekinumab 45 mg (1 of 209, 0.5%) and 90 mg (3 of 347, 0.9%) groups reported a major cardiovascular event.
- Among subjects in the etanercept group, 3 of 347 (0.9%) subjects reported a major cardiovascular event: 1 (0.3%) occurred prior to crossover and 2 (2 of 291, 0.7%) occurred after crossover.

Malignancies

- Through Week 64, comparable rates of malignancies were reported in the ustekinumab 45 mg (4 of 209, 1.9%) and 90 mg (8 of 347, 2.3%) groups. Four subjects reported malignancies other than nonmelanoma skin cancer (NMSC) and 8 subjects reported an NMSC. The majority of NMSCs were basal cell cancers.
- In the etanercept group, 2 of 347 (0.6%) subjects reported malignancies after crossover to ustekinumab 90 mg.

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Injection-site Reactions to Ustekinumab

- The proportion of subjects in the ustekinumab group who experienced an injection-site reaction was 2.3% following placebo administration, 4.3% following ustekinumab 45 mg administration, and 3.7% following ustekinumab 90 mg administration.
- In subjects crossing over from etanercept to ustekinumab, 1 (0.3%) subject experienced an injection-site reaction following administration of placebo and 4 (1.4%) subjects experienced an injection-site reaction following administration of ustekinumab 90 mg.

Adverse Events of Psoriasis

- Through Week 64, similar proportions or subjects in the ustekinumab 45 mg (3.3%) and 90 mg (2.0%) groups were reported to have AEs of psoriasis; all subjects were reported to have a worsening or exacerbation of psoriasis.
- In the etanercept group, AEs of psoriasis were reported in 1.4% of subjects prior to crossover and 1.7% of subjects after crossover to ustekinumab 90 mg. All subjects had worsening or exacerbation of psoriasis.

Laboratory Test Results

Through Week 64, rates of markedly abnormal hematology and chemistry labs were low and generally transient. No clear pattern of changes over time was observed.

Injection-site reactions and Antibodies to Ustekinumab

There was no apparent association between development of antibodies to ustekinumab and development of injection-site reactions.

Conclusions:

- In subjects who were PGA responders at Week 12, ustekinumab subjects maintained a PGA response of cleared, minimal, or mild longer compared with etanercept subjects.
- The majority of ustekinumab subjects who experienced a recurrence of their psoriasis after treatment interruption reachieved a PGA response after retreatment.
- An additional dose of ustekinumab at Week 16 converted a substantial proportion of PGA nonresponders to PGA responders.
- The majority of etanercept responders who experienced a recurrence of their psoriasis after treatment interruption became PGA responders after crossover to ustekinumab.
- The majority of subjects who were PGA nonresponders in the etanercept group became PGA responders when treated with ustekinumab.
- Ustekinumab therapy was well tolerated through Week 64.
- No safety concerns were identified in subjects initially treated with etanercept who crossed over to ustekinumab.
- Antibodies to ustekinumab developed at a low rate through Week 64.

Date of Report: 15 Aug 2009

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