2 Synopsis

<table>
<tr><td>Name of sponsor:
Janssen Pharmaceutical K.K.</td><td rowspan="3">Summary tale of the study
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Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Generic name:
Not determined</td></tr>
<tr><td>Name of active ingredient:
CNTO 1275</td></tr>
<tr><td colspan="3">Study title:
A Placebo-Controlled Double-Blind Comparative Study of CNTO 1275 in Subjects with Plaque Psoriasis</td></tr>
<tr><td colspan="3">Principal Investigator:
Osamu Nemoto, Clinic Director, Sapporo Skin Clinic and others, totally 35 personnels (See attachment 16.1.4a)</td></tr>
<tr><td colspan="3">Study Centers:
Sapporo Skin Clinic, and others, totally 35 sites(See attachment 16.1.4a)</td></tr>
<tr><td colspan="3">Publication (reference): none</td></tr>
<tr><td colspan="2" rowspan="2">Study period:
First day of obtaining informed consent: March 24, 2008
Day of observation on last subject: study ongoing
Day of observation on Week 28 on last subject: April 28, 2009</td><td>Phase of development:
Phase II/III</td></tr>
<tr><td>Type of study:
Verification study</td></tr>
<tr><td colspan="3">Study objectives:
The objective of this study is to assess the efficacy and safety of CNTO 1275 in Japanese subjects with moderate to severe plaque psoriasis in subcutaneous administration at two doses of 45 mg and 90 mg at weeks 0 and 4 and then every 12 weeks, using placebo as a control, and also to assess the efficacy and safety of long term administration up to 52 weeks. In addition, the pharmacokinetics (including the measurement of serum anti-CNTO 1275 antibodies) is assessed.</td></tr>
<tr><td colspan="3">Study method:
This study is a multicenter, double-blind (double-dummy method), randomized, placebo-controlled, parallel group comparative study of CNTO 1275 subcutaneously administered to subjects with moderate to severe plaque psoriasis.
The efficacy and safety over 12-week treatment with subcutaneous administration of CNTO 1275 at 45 mg or 90 mg were evaluated using placebo as a control. Subjects in the placebo group were subcutaneously administered with CNTO 1275 (45 mg or 90 mg) in blinded manner from week 12 to Week 52. The long-term safety and efficacy were assessed in CNTO 1275 45 mg group, CNTO 1275 90 mg group, and the groups switched from placebo group.
The primary endpoint was the percentage of subjects who achieved ≥75% improvement in psoriasis area and severity index (PASI) score at 12 weeks of treatment. Major secondary endpoints were physician’s global assessment (PGA) and change in dermatology life quality index (DLQI) at week 12. Safety endpoints were adverse events, reasonably related adverse events and injection site reactions. The pharmacokinetics endpoints were profiles of serum CNTO1275 and production of anti-CNTO1275 antibodies.</td></tr>
<tr><td colspan="3">Number of subjects (at planning and analysis):
At planning: 150 (60 in 45 mg group, 60 in 90 mg group, 30 in placebo group)
At analysis: number of subjects allocated: 160 subjects (including 2 subjects who discontinued the study prior to the start of administration of the investigational drug)
1) Population for efficacy analysis
- Maximum population for analysis (full analysis set; FAS, hereafter): 157 subjects
- Population for analysis who matched to the study protocol (per-protocol set; PPS, hereafter): 151 subjects
2) Population for safety analysis (safety population; (SP)): 158 (Week 0 to 12), 154 (Week 0 to 28)
3) Population for pharmacokinetics analysis
- Population for pharmacokinetics: 158
- Population for immunogenicity: 156</td></tr>
<tr><td colspan="3">Diagnosis and Inclusion Criteria:
Subjects had to be patients with moderate to severe plaque psoriasis (psoriasis vulgaris and psoriatic arthritis) who met all of the following criteria.

1)Patients who were given sufficient explanation about the investigational product and the study prior to the conduct of the study, and gave their own consent to participate in the study in writing.
2)Patients at least 20 years of age at the time of informed consent (regardless of gender and in-/out- patient status)
3)Patients diagnosed with psoriasis (psoriasis vulgaris or psoriatic arthritis) at least 6 months before the subject registration</td></tr>
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4) Patients with plaque psoriasis covering at least 10% of total body surface area (BSA) at the time of informed consent and at registration
5) Patients with a PASI score of ≥12 at the time of informed consent and at registration
6) Patients who can receive phototherapy or systemic therapy for psoriasis (with or without a history of the relevant therapy)
7) If the patient is a female with child-bearing potential or a male partner of a female with child-bearing potential, the patient must agree to take an appropriate contraceptive measure such as condoms and oral contraceptives from the day of informed consent for 1 year after the final treatment with the investigational product. Females with child-bearing potential must be negative for pregnancy test at screening.
8) Patients who agree not to receive BCG vaccination and live vaccine inoculation (bacteria or virus) for 1 year after the final treatment with the investigational product

Investigational Products, Dosages, and Lot Number:

- Investigational products: CNTO 1275 (test drug) and placebo (control drug)
- Dosage and treatment methods:

The subjects were randomly assigned to one of three treatment groups. Since the double-dummy method was employed in this study, two prefilled syringes per dosing were subcutaneously administered to subjects during the treatment period. In the active drug treatment period starting from Week 12, CNTO 1275 was administered to all subjects.

Placebo-controlled treatment period (Weeks 0 - 12)

- 45-mg group: subcutaneous (SC) treatment with CNTO 1275 45 mg (0.5 mL) or placebo (1.0 mL) at Weeks 0 and 4.
- 90-mg group: subcutaneous (SC) treatment with CNTO 1275 90 mg (1.0 mL) or placebo (0.5 mL) at Weeks 0 and 4.
- Placebo group: SC treatment with placebo (0.5 mL and 1.0 mL) at Weeks 0 and 4.

Active drug treatment period (Weeks 12 - 64)

- 45-mg group: SC treatment with placebo (0.5 mL and 1.0 mL) at Week 12, followed by SC treatment with CNTO 1275 45 mg (0.5 mL) and placebo (1.0 mL) at Week 16. Subsequently, SC treatment with CNTO 1275 45 mg (0.5 mL) and placebo (1.0 mL) every 12 weeks up to Week 52 (i.e., 3 administrations on Week 28, 40 and 52)
- 90-mg group: SC treatment with placebo (0.5 mL and 1.0 mL) at Week 12, followed by SC treatment with CNTO 1275 90 mg (1.0 mL) and placebo (0.5 mL) at Week 16. Subsequently, SC treatment with CNTO 1275 90 mg (1.0 mL) and placebo (0.5 mL) every 12 weeks up to Week 52 (i.e., 3 administrations on Week 28, 40 and 52)
- Placebo group: At Weeks 12 and 16, SC treatment with CNTO 1275 and placebo in subjects divided into the following 2 groups. Subsequently, SC treatment with CNTO 1275 at the same dose and placebo every 12 weeks up to Week 52 (i.e., 3 administrations on Week 28, 40 and 52)
  Placebo group a: CNTO 1275 45 mg (0.5 mL) and placebo (1.0 mL)
  Placebo group b: CNTO 1275 90 mg (1.0 mL) and placebo (0.5 mL)

Subjects in the placebo group were assigned to placebo group A or B at the same time when they were randomized to the placebo group at registration. At Week 28, nonresponders (< 50% improvement in PASI score from baseline) were withdrawn from treatment with the investigational product.

Lot Number: (The lot numbers and expiration dates of CNTO1275 and placebo were identical for every syringe)

- Prefilled syringe for 0.5 mL: 03HB (Expiration date: December, 17, 2008)
  05HF (Expiration date: January, 15, 2010)
- Prefilled syringe for 1.0 mL: 04HB (Expiration date: December, 17, 2008)
  06HF (Expiration date: January, 15, 2010)

Study Period:

78 weeks (Screening period: approximately 6 weeks at the maximum, Efficacy assessment period: 64 weeks, Follow-up assessment period: 8 weeks). This report is an interim report based on the data obtained from initial administration to Week 28.

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Endpoints:

Efficacy endpoints:

1) Primary endpoint: The percentage of subjects who achieved ≥75% improvement in PASI score at Week 12 [Percentage of subjects who achieved ≥75% improvement in PASI score at Week 12 from baseline (Week 0)]
2) Major secondary endpoints:
   a) The percentage of subjects who achieved physician's global assessment (PGA) scores of "0 (cleared) or 1 (minimal)" at Week 12
   b) The change in DLQI score from baseline at Week 12

Safety endpoints:

1) Adverse events
2) Reasonably related adverse events *
3) Injection site reactions

Pharmacokinetics endpoints:

1) Serum CNTO 1275 concentration
2) Anti-CNTO 1275 antibodies

Statistical Analyses:

1) Subject characteristics

Calculation of descriptive statistics and frequency tabulation for demographic characteristics and other baseline characteristics were performed in FAS and SP and summarized by treatment group.

2) Primary endpoints

Statistical analyses were conducted mainly for FAS.

a) Primary endpoint

The percentage of subjects with ≥75% improvement in PASI score at Week 12 were compared between the placebo group and the 45 mg group and between the placebo group and the 90 mg group by Fisher's exact test. The testing was performed using Holm's method to control the overall type-I error at ≤0.05.

b) Major secondary endpoints

1. The percentages of subjects who achieved PGA score of "0 (cleared) or 1 (minimal)" at Week 12 were compared between the placebo group and the 45 mg group and between the placebo group and the 90 mg group by Fisher's exact test. The testing was performed using Holm's method as with the primary endpoint.
2. Change from baseline in DLQI score at Week 12 was compared between the placebo group and the 45 mg group and between the placebo group and the 90 mg group using the 2-sample t-test. The testing was performed using Holm's method as with the primary endpoint.

3) Safety analysis

For all treatment-emergent signs and symptoms (TESS), the number of subjects with events, the number of events, and the incidence rate were calculated by system organ class (SOC) and preferred term (PT) using MedDRA/J (Ver.11.1) for analyses of adverse events in SP.

For laboratory test values and vital signs, descriptive statistics were calculated for quantitative test values at each testing time point, and changes in qualitative test values from the initiation of treatment with the investigational product were tabulated as shift tables.

4) Pharmacokinetics analysis

Descriptive statistics [number of subjects, mean, standard deviation, coefficient of variance, median, interquartile range, and range (minimum and maximum)] were calculated by blood sampling time and dose (treatment pattern) using measured values of serum CNTO 1275 concentrations obtained from the pharmacokinetics population. Changes over time in serum CNTO 1275 concentrations were graphed using the obtained descriptive statistics.

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Summary – Conclusion:

Efficacy:

- The percentages of subjects who achieved the primary efficacy endpoint of PASI 75 response at Week 12 (the primary endpoint) were significantly higher in both 45 mg and 90 mg groups than in the placebo group, which showed that the efficacy of each of CNTO 1275 45 mg and 90 mg was superior to that of placebo.
- Comparison of distribution of PASI and PGA scores, measured as indices for efficacy against psoriasis, among treatment groups showed better improvement in each CNTO 1275 group compared with placebo, demonstrating improvement of psoriasis by treatment with CNTO 1275.
- Better improvement in quality of life as measured by DLQI, 36-item short form health survey (SF-36) and psoriasis disability index (PDI) was observed in each CNTO 1275 group compared with placebo.
- Improvement in psoriasis appeared in each CNTO 1275 group from Week 2, as judged by changes over time in the percent improvement in PASI score, in the percentages of subjects achieving PASI 50, PASI 75 or PASI 90 response, and in the percentages of subjects with PGA scores of "0 (cleared)," "0 (cleared) or 1 (minimal)," or "0 (cleared), 1 (minimal) or 2 (mild)".
- The percentage of subjects achieving PASI 50, PASI 75 or PASI 90 response, and the percentage of subjects with PGA scores of "0 (cleared)," "0 (cleared) or 1 (minimal)," or "0 (cleared), 1 (minimal) or 2 (mild)" continuously increased in each CNTO 1275 group with time from treatment start. The improvement in psoriasis observed at Week 12 was maintained through Week 28. Therefore, the efficacy of CNTO 1275 in improving psoriasis was thought to persist through Week 28.
- The changes from baseline in DLQI score, SF-36 and PDI were significantly higher in each CNTO 1275 group compared with placebo at Week 12, and generally maintained through Week 28. Therefore, the efficacy of CNTO 1275 in improving the subject's QOL was thought to be maintained through Week 28.
- Improvements in nail psoriasis and joint pain measured by nail psoriasis severity index (NAPSI) and visual analog scale (VAS) were suggested.
- Subgroup analyses suggested a tendency of lower efficacy with increase in body weight, but the efficacy was observed in all subpopulations evaluated.

Safety:

- Rates of adverse events or reasonably related adverse events in the 45 mg and in the 90 mg groups were comparable to those in the placebo group from Week 0 through Week 12.
- There were no significant differences in rates of adverse events or reasonably related adverse events between the 45 mg group and the 90 mg group through Week 12, as well as through Week 28.
- Frequent adverse events in 154 subjects of the combined active drug group through Week 28 were nasopharyngitis 39.0% (60/154), increased blood triglycerides 9.7% (15/154), increased blood creatinine phosphokinase 7.1% (11/154), increased eosinophil count 6.5% (10/154) and seasonal allergy 5.2% (8/154).
- No death occurred in this study. Serious adverse events that occurred after CNTO 1275 administration were pneumonia, prostate cancer, psoriasis, osteonecrosis, abnormal electrocardiogram, and fall in 1 episode in 1 subject each, and dislocation of joint prosthesis in 2 episodes in 1 subject.
- Incidence of injection site reactions was low at 0.9% (4/428), all of which were mild in severity.

Pharmacokinetics:

- After subcutaneous administration of CNTO 1275 45 mg or 90 mg, serum concentrations of CNTO 1275 increased in proportion to dose.
- The serum CNTO 1275 concentration was shown to have reached the steady state by Week 28. It was suggested that high body weight, diabetes and antibodies to CNTO 1275 decreased serum CNTO 1275 concentration.

Immunogenicity:

- After subcutaneous administration of CNTO 1275, 5.9% (9/153) of 153 subjects were positive for antibodies to CNTO 1275.
- Majority of antibody positive subjects had titers $\leq$ 1:80. No allergic reactions including anaphylaxis were observed in the antibody positive subjects.

Conclusions:

From the study, the following conclusions on efficacy and safety of CNTO 1275 were obtained.

- Treatment with CNTO 1275 improved psoriasis.

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- Treatment with CNTO 1275 improved QOL in psoriasis patients.
- Treatment with CNTO 1275 exhibited efficacy against dermal symptoms from the early stage of treatment (Week 2).
- Improvements in psoriasis and QOL observed at Week 12 were maintained through Week 28.
- Efficacy of CNTO 1275 on nail psoriasis and joint pain were suggested.
- Serum concentrations of CNTO 1275 increased in proportion to dose.
- The safety profile of CNTO 1275 was comparable to that of placebo through Week 12, while the rate of mild infections was slightly higher in CNTO 1275 groups than in the placebo group. Treatment with CNTO 1275 was generally well tolerated through Week 28.
- Increase in dosage was not accompanied by any increase in incidence of adverse events, with similar patterns of type and severity.

Date of reporting: October 27, 2009

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