2. Synopsis

<table>
<tr><td>Name of sponsor:
Janssen Pharmaceutical K.K.</td><td rowspan="3">Summary table of the study Corresponding parts of the application materials
Number of separate volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Generic name:
To be 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 Type Psoriasis</td></tr>
<tr><td colspan="3">Investigators:
Osamu Nemoto, Clinic Director, Sapporo Skin Clinic and others, 35 investigators in total (See Attachment 16.1.4a)</td></tr>
<tr><td colspan="3">Study Centers:
Sapporo Skin Clinic, and others, 35 sites in total (See Appendix 16.1.4a)</td></tr>
<tr><td colspan="3">Publication: none</td></tr>
<tr><td colspan="2" rowspan="2">Study period:
First day of obtaining informed consent: March 24, 2008
Last day of observation on last subject: March 9, 2010</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 in this study is to assess the efficacy and safety of CNTO 1275 in Japanese subjects with moderate to severe plaque type 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), randomized, placebo-controlled, parallel group comparative study of CNTO 1275 subcutaneously administered in subjects with moderate to severe plaque type psoriasis.
The efficacy and safety over 12-week treatment with subcutaneous administration of CNTO1275 at 45 mg or 90 mg were evaluated using placebo as a control. Subjects in placebo group were subcutaneously administered CNTO1275 (45mg or 90 mg) in blinded manner from week 12 to Week 52. The long-term safety and efficacy were assessed in CNTO1275 45 mg group, CNTO1275 90 mg groups, and the groups switched from placebo group.
The primary efficacy endpoint was the percentage of subjects who achieved ≥75% improvement in psoriasis area and severity index (PASI) at week 12 of treatment. Main secondary endpoints were physician's global assessment (PGA) and change in dermatology life quality index (DLQI) at week 12. Safety endpoints were adverse events, adverse drug reactions, 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 (planned and analyzed):
Planned: 150 (60 in 45 mg group, 60 in 90 mg group, 30 in placebo group)
Analyzed: number of subjects allocated: 160 subjects (including 2 subjects who discontinued the study prior to the start of the investigation drug administration)
1) Population for efficacy analysis
• Maximum population for analysis (full analysis set [FAS]): 157 subjects
• Population for analysis who fulfilled the study protocol (per protocol set [PPS]): 151 subjects
2) Population for safety analysis (safety population [SP]): 158 (Week 0 to 12), 154 (Week 0 to 72)
3) Population for pharmacokinetics analysis
• Population for pharmacokinetics analysis: 158
• Population for immunogenicity analysis: 156</td></tr>
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Name of sponsor: Janssen Pharmaceutical K.K.	**Summary table of the study** **Corresponding parts of the application materials** **Number of separate volume:** **Page:**	(For National Authority Use only)
Generic name: To be determined		
Name of active ingredient: CNTO 1275		

Diagnosis and Inclusion Criteria:

Subjects had to be patients with moderate to severe plaque type psoriasis (psoriasis vulgaris or psoriatic arthritis) who met all of the following criteria:

1) Patients who were given a 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
4) Patients with plaque type 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 until 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 a final treatment with the investigational product

Investigational Products, Dosages, and Lot Number:

- Investigational products: CNTO1275 (test drug) and placebo (control drug)
- Dosage and treatment methods:

  The subjects were randomly assigned to one of the following treatment groups. Since the double-dummy method was employed in this study, two prefilled syringes per dosing were subcutaneously administered to subjects.
  - 45-mg group: CNTO 1275 45 mg (0.5 mL) and placebo (1.0 mL) were administered subcutaneously at week 0, week 4, and then every 12 weeks up to week 52 (i.e., 4 administrations at weeks 16, 28, 40 and 52). In addition, placebo (0.5 mL and 1.0 mL) was administered subcutaneously at week 12.
  - 90-mg group: CNTO 1275 90 mg (1.0 mL) and placebo (0.5 mL) were administered subcutaneously at week 0, week 4, and then every 12 weeks up to week 52 (i.e., 4 administrations at weeks 16, 28, 40 and 52). In addition, placebo (0.5 mL and 1.0 mL) was administered subcutaneously at week 12.
  - Placebo group a: Placebo (0.5 mL and 1.0 mL) was administered subcutaneously at week 0 and week 4, followed by subcutaneous administration of CNTO 1275 45 mg (0.5 mL) and placebo (1.0 mL) at week 12, week 16, and then every 12 weeks up to week 52 (i.e., 3 administrations at weeks 28, 40 and 52).
  - Placebo group b: Placebo (0.5 mL and 1.0 mL) was administered subcutaneously at week 0 and week 4, followed by subcutaneous administration of CNTO 1275 90 mg (1.0 mL) and placebo (0.5 mL) at week 12, week 16, and then every 12 weeks up to week 52 (i.e., 3 administrations at weeks 28, 40 and 52).

- 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 period: 8 weeks). Results of the placebo-controlled study on CNTO 1275 45 mg and 90 mg were described in the28-Week Clinical Study Report. This report is the final report based on the data obtained from the long-term administration of CNTO 1275 45 mg and 90 mg through week 52.

Name of sponsor: Janssen Pharmaceutical K.K.	**Summary table of the study** **Corresponding parts of the application materials** **Number of separate volume:** **Page:**	(For National Authority Use only)
Generic name: To be determined		
Name of active ingredient: CNTO 1275		

Endpoints:

Efficacy endpoints:

Efficacy endpoints evaluated in this report were effect on dermal symptoms evaluated by PASI and PGA, effect on nail psoriasis evaluated by NAPSI and number of nails involved by psoriasis, effect on joint symptoms evaluated by pain assessment (VAS), and effect on QOL evaluated by DLQI, SF-36, and PDI.

Safety endpoints:

1) Adverse events
2) Adverse drug reactions
3) Injection site reactions

Pharmacokinetics:

1) Serum CNTO1275 concentration
2) Anti-CNTO1275 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) Efficacy

Statistical analyses were conducted mainly for FAS. The following efficacy endpoints were evaluated in this report:

(i) PASI score
(ii) PASI score improvement rate
(iii) Percentage of subjects achieving ≥50%, ≥75%, ≥90%, or 100% improvement in PASI score
(iv) Percentages of subjects with PGA score rated “0 (cleared)”, “1 (minimal) or less” , and “2 (mild) or less”
(v) DLQI [DLQI score and change in DLQI score]
(vi) Change in SF-36 score
(vii) Change in PDI score
(viii) Improvement rate in nail psoriasis severity index (NAPSI) score
(ix) Change in the number of nails involved by psoriasis
(x) Change in VAS of joint symptoms

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) 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 CNTO1275 concentration obtained from the pharmacokinetics population. Changes over time in serum CNTO1275 concentrations were graphed using the obtained descriptive statistics.

Name of sponsor: Janssen Pharmaceutical K.K.	**Summary table of the study** **Corresponding parts of the application materials** **Number of separate volume:** **Page:**	(For National Authority Use only)
Generic name: To be determined		
Name of active ingredient: CNTO 1275		

Summary – Conclusions:

CNTO 1275 was administered for 12 weeks in two dosage levels, 45 mg and 90 mg, to patients with moderate to severe plaque type psoriasis to evaluate the efficacy and safety using placebo as the control. Also, CNTO 1275 was administered at 45 mg or 90 mg up to week 52 to evaluate the efficacy and safety. The percentage of subjects who achieved the primary endpoint or PASI score improvement of ≥75% at week 12 was significantly higher in the 45 mg group and the 90 mg group than in the placebo group ($p<0.0001$ in Fisher's exact test for both comparisons). As regards safety, the incidences of adverse events and adverse drug reactions from week 0 through 12 in the 45 mg group and in the 90 mg group were comparable to those in the placebo group. No significant difference was observed in the incidence of adverse events or adverse drug reactions between 45 mg group and 90 mg group. Moreover, comparison of the incidence of adverse events or adverse drug reactions from week 0 through 28 showed no significant difference between the 45 mg group and the 90 mg group. This report is the final report of this clinical study based on the data of the final analysis. The above results based on the data obtained up to week 28 including the 12-week placebo control period were described in the 28-Week Clinical Study Report. Below are described the results of efficacy and safety in continued administration of CNTO 1275 at 45 mg or 90 mg up to week 52.

The efficacy and safety analysis sets in this report were 157 subjects in FAS (placebo→45 mg group: 15, placebo→90 mg group: 16, 45 mg group: 64, 90 mg group: 62) and 158 subjects in SP (placebo group: 32, 45 mg group: 64, 90 mg group: 62).

Efficacy:

The percentages of subjects who achieved the primary endpoint or PASI score improvement of ≥75% at week 12 was 59.4% and 67.7% in the 45 mg group and the 90 mg group, respectively, which were significantly higher than the percentage in the placebo group. The percentages of subjects who achieved PASI score improvement of ≥75% increased gradually from week 12 and remained at a roughly constant level. Comparison between dose groups showed that the percentages of subjects who achieved PASI score improvement of ≥75% was not significantly different between the 45 mg group and the 90 mg group at week 28, whereas from week 28 the percentage remained at around 70% in the 45 mg group but, in the 90 mg group, it further increased up to approximately 80%, resulting in approximately 10% higher rate in the 90 mg group than in the 45 mg group.

The percentage of subjects who achieved PASI score improvement of ≥50% or ≥90% remained at a roughly constant level up to week 64 although slight fluctuations were observed after week 28. Comparison between dose groups showed that the percentage of subjects who achieved PASI score improvement of 90% or more was approximately 10% higher in the 90 mg group than in the 45 mg group at week 12, and the difference further increased thereafter, with the percentage being approximately 15% higher in the 90 mg group than in the 45 mg group at all evaluation time points except week 64. The percentage of subjects who achieved PASI score improvement of ≥50% was comparable between the 45 mg group and the 90 mg group from week 12 up to week 64.

According to the evaluation by PGA, the percentage of subjects with PGA rated "0 (cleared) or 1 (minimal)" or "2 (mild) or less" remained at a roughly constant level up to week 64 both in 45 mg group and 90 mg group although slight fluctuations were observed. Comparison between dose groups showed that the percentage was higher in the 90 mg group than in the 45 mg group at almost all evaluation time points.

In the placebo→45 mg group and in the placebo→90 mg group, both PASI and PGA scores improved after placebo was switched to CNTO 1275 at week 12 and reached to the improvement rates comparable to those observed in the 45 mg group and the 90 mg group by around week 28. However, the percentage of subjects who achieved PASI score improvement of ≥50% remained lower compared with the 45 mg group and the 90 mg group, with the percentage being particularly low in the placebo→90 mg group. There were only 15 and 13 subjects in the placebo→45 mg group and in the placebo→90 mg group, respectively, In addition, 3 subjects in the placebo→45 mg group and 5 subjects in the placebo→90 mg group were judged to be treatment failure during the placebo-control period up to week 12, and were handled as not having achieved subsequent endpoints. These factors are likely to have caused the observed differences in the percentage of PASI and PGA score improvement.

Name of sponsor: Janssen Pharmaceutical K.K.	Summary table of the study Corresponding parts of the application materials Number of separate volume:	(For National Authority Use only)
Generic name: To be determined		
Name of active ingredient: CNTO 1275	**Page:**	

Changes in the total scores or in the summary scores of DLQI, SF-36 and PDI remained at roughly constant levels from week 12 up through week 64, showing no significant difference between the 45 mg group and the 90 mg group.

NAPSI score improvement rate and the change in the number of nails involved by psoriasis improved continuously through week 64 in all CNTO 1275 groups. In patients who had joint symptoms before the start of investigational product administration, pain VAS of joint symptoms showed a roughly constant level of improvement from week 12 through week 64.

Following repeated administration of CNTO 1275 at 45 mg and 90 mg, the median serum CNTO 1275 concentration increased roughly in proportion to dose, and the trough serum CNTO 1275 concentration remained at a roughly constant level through week 64.

The percentage of subjects who turned positive for anti-CNTO 1275 antibody by week 72 was 6.5% (10/153), and the titer was 80 fold or less in 7 out of the 10 antibody-positive subjects. Serum CNTO 1275 concentration at weeks 40, 52 and 64 was lower in anti-CNTO 1275 antibody-positive subjects than in antibody-negative subjects, being BQL in all subjects except 1 out of 6 anti-CNTO 1275 antibody-positive subjects in the 45 mg group who showed a serum CNTO 1275 level at week 64. In the 45 mg group, the percentage of subjects who achieved PASI score improvement of ≥75% or ≥90% at week 64 tended to be lower in anti-CNTO 1275 antibody-positive subjects than in antibody-negative subjects, whereas the percentage of subjects who achieved PASI score improvement of ≥50% was high both in antibody-positive and negative subject groups.

When subjects who achieved PASI score improvement of ≥75% at week 28 and had PASI evaluated at week 64 (45 mg group: 43 subjects, 90 mg group: 40 subjects) were classified into subgroups by PASI score improvement rate at week 64 (<50% [no response group], 50%≤ <75% [partial response group], and ≥75% [complete response group]), only one subject in the 45 mg group belonged to the no response group. This subject was handled as a no response case after being judged as a case of treatment failure because of the use of a prohibited concomitant drug (Rinderon suspension for injection) to treat a complication (lumbago) at week 56. Given that PASI score improvement rate in this subject was ≥75% until the subject was judged to be a case of treatment failure, the treatment effect did not decrease detectably after week 28 in any of subjects with PASI score improvement rate of ≥75% at week 28. Investigation of serum CNTO 1275 concentration from week 28 in each subgroup showed that, in the 45 mg group, the concentration was lower in the partial response group (7 subjects) than in the complete response group at all evaluation time points including week 28, but the concentration did not show any tendency to decrease from week 28. In the 90 mg group, serum CNTO 1275 concentration apparently tended to be lower in the partial response group (2 subjects) than in the complete response group, but no detailed comparison could be performed because of the limited number of the subjects.

Safety:

The incidences of adverse events and adverse drug reactions through week 72 were 97.4% (150/154 subjects, 1022 episodes) and 88.3% (136/154 subjects, 720 episodes). The incidence of adverse events by dose group was 96.9% (62/64) in the 45 mg group and 98.4% (61/62) in the 90 mg group, showing no significant difference between the two groups. The incidence of adverse events in the placebo→45 mg group and the placebo→90 mg group was 93.3% (14/15) and 100.0% (13/13), respectively.

The most frequent adverse event in the combined active drug group was nasopharyngitis (55.2%, 85/154). Other adverse events observed in the combined active drug group with incidence of ≥10% were increased blood triglycerides, increased blood creatinine phosphokinase, and seasonal allergy. These frequent adverse events showed similar tendencies as those observed up to week 28, with the incidences showing no clear difference between the 45 mg group and the 90 mg group or between the placebo→45 mg group and the placebo→90 mg group.

Investigation of adverse events by the time of onset showed that the incidence of any of adverse events did not increase with the duration of exposure.

Throughout the study period, no death occurred. Other serious adverse events occurred in 8.4% (13/154, 18 episodes) of the combined active drug group, including cataract and fall in 2 subjects each. There were no other serious adverse events that occurred in more than one subject. Adverse events that resulted in the

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Generic name: To be determined		
Name of active ingredient: CNTO 1275	**Page:**	

discontinuation of administration were reported in 3.9% (6/154, 6 episodes) of subjects in the combined active drug group. There was no clear difference in the incidence of infection between dose groups. Serious infection was reported in 3 subjects of the combined active drug groups, but there were no cases of tuberculosis or opportunistic infection. Malignant tumor was reported in 2 subjects of the combined active drug group. Neither anaphylactic reaction nor serum sickness-like reaction was observed. The incidence of injection site reactions, which is the theoretically predicted risk of protein preparations for subcutaneous injection, was low at 0.8% (7/847 doses), and all reactions observed were mild in severity. Among the events investigated as important adverse events of CNTO 1275, i.e., those related to cardiovascular system, to psoriasis, to psoriatic arthritis, or to asthma, there were no adverse events of particular clinical significance.

No injection site reactions occurred in any of antibody-positive patients, failing to show any clear relationship between the presence of anti-CNTO 1275 antibody and the safety.

As regards hematological test, blood biochemistry test, other blood test, and urinalysis, no clinically significant changes were observed in any of the parameters tested including blood triglycerides and blood creatinine phosphokinase, parameters with high incidences of adverse events. No clear difference was observed in the parameter values between the dose groups. Nor were there any clear differences in vital signs or electrocardiogram between the dose groups, showing no consistent tendency caused by the administration of the investigational product.

Conclusion:

CNTO 1275 was administered at a dose of 45 mg or 90 mg to patients with moderate to severe plaque type psoriasis at week 0, week 4, and then every 12 weeks through week 52. The treatment effects on psoriasis and QOL at week 12 were significantly greater in both dose groups than in the placebo group, and remained at roughly constant levels without decrease through week 64. The effect on psoriasis tended to be greater in the 90 mg group than in the 45 mg group, with a clear difference being observed from week 28.

Throughout the period up to week 20 after the last administration (week 72 from treatment start), CNTO 1275 was well tolerated. Safety profile was generally favorable in both dose groups.

Date of reporting: July 26, 2010

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