



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)	
Name of Study Drug: Adalimumab (D2E7, LU200134)			Volume:
Name of Active Ingredient: Adalimumab			Page:
Title of Study: A Phase 2/3, Randomized, Double-Blind, Placebo Controlled, Multicenter Study of Efficacy and Safety of Adalimumab (D2E7) in Japanese Subjects with Moderate to Severe Chronic Plaque Psoriasis			
Study Sites: Multicenter, 43 study sites in Japan.			
Studied Period: 24 weeks		Phase of Development: 2/3	
First Subject First Dose:	02 Nov 2005		
Last Subject Last Dose:	06 Dec 2006		
Last Study Procedure Date:	13 Dec 2006		
Objectives: <p>The objective of this study was to determine the efficacy and safety of three different dosage regimens (80 mg every other week [eow] and 40 mg eow with and without a loading dose of 80 mg) of subcutaneous (<i>sc</i>) administered adalimumab vs. placebo in the treatment of adult Japanese subjects with moderate to severe chronic plaque psoriasis over a 24-week period. The study also investigated the benefits of a single loading dose of 80 mg in the 40 mg eow dosage groups. Pharmacokinetics and immunogenicity of adalimumab following <i>sc</i> injection were also assessed.</p> <p>This report focuses on assessment of the pharmacokinetics and immunogenicity of adalimumab. A population pharmacokinetic analysis of serum adalimumab concentrations was carried out to quantify potential differences in adalimumab pharmacokinetics between Japanese subjects with moderate to severe chronic plaque psoriasis (Study M04-688) and Japanese subjects with rheumatoid arthritis (RA) (Study M02-575).</p>			



Methodology:

This study was a multi-center, Phase 2/3, randomized, double-blind, placebo-controlled study designed to evaluate the clinical efficacy and safety of adalimumab vs. placebo and the benefits of a single loading dose of 80 mg adalimumab in the treatment of adult Japanese subjects with moderate to severe chronic plaque psoriasis. The study included a screening period for up to 6 weeks, a blinded 24-week treatment period with a primary endpoint at Week 16 where efficacy was assessed by measuring the Psoriasis Area and Severity Index (PASI) 75 response. After the completion of Study M04-688, subjects were eligible to rollover to the 28-week extension Study M04-702.

Approximately 160 adult Japanese subjects with moderate to severe chronic plaque psoriasis with an affected body surface area (BSA) $\geq 10\%$ and a PASI score ≥ 12 were to be enrolled.

Subjects who met all of the inclusion criteria and none of the exclusion criteria at the baseline were randomized 1:1:1:1 to one of the four treatment regimens. Subjects randomized to Regimen A received 40 mg adalimumab eow starting at baseline (Week 0). Subjects randomized to Regimen B received 80 mg adalimumab at baseline then 40 mg eow starting at Week 2. Subjects randomized to Regimen C received 80 mg adalimumab eow starting at baseline. Subjects randomized to Regimen D received placebo eow starting at baseline.

Blood samples were obtained prior to study drug injection at baseline and at Weeks 2, 4, 8, 12, 16, 20 and 24, or at Early Termination and the Follow-up visits, if applicable, for the evaluation of serum adalimumab concentration. Blood samples were also obtained prior to study drug injection at baseline and at Weeks 16 and 24, or at Early Termination and the Follow-up visits, if applicable, for the evaluation of serum anti-adalimumab antibodies (AAA).

Adalimumab was analyzed at MDS Pharma Services Switzerland AG and AAA samples were analyzed at Abbott GmbH & Co. (Ludwigshafen, Germany). The limit of quantitation (LOQ) for adalimumab was established at 2.5 ng/mL in diluted serum or 25 ng/mL in undiluted serum. The LOQ for AAA was established at 0.5 ng/mL in diluted serum or 5 ng/mL in undiluted serum. To meet assay criteria, only samples in which the adalimumab concentration was low ($< 2 \mu\text{g/mL}$) were to be selected for AAA assay. Serum samples were considered to be positive for AAA (AAA+) if all of the following criteria were met: the measured AAA concentration was greater than 20 ng/mL; the signal was reduced by $< 50\%$ by addition of 10% human serum; and the serum sample was collected within 30 days after an adalimumab dose.



Number of Subjects (Planned and Analyzed):

Planned: 160; Entered: 169; Completed: 147.

The following table summarizes the disposition of subjects in the study.

Treatment Group	Number of Subjects Randomized	Number (%) of Subjects Completed 24 Weeks
40 mg eow	38	34 (89.5)
80 mg at Week 0, 40 mg eow from Week 2	43	35 (81.4)
80 mg eow	42	38 (90.5)
Placebo	46	40 (87.0)

The summary demographics for all subjects who entered the study are shown in the following table.

	Adalimumab-Treated Subjects				All Adalimumab (N = 123)
	Placebo (N = 46)	40 mg eow (N = 38)	40 mg eow with an 80 mg loading (N = 43)	80 mg eow (N = 42)	
	Mean ± SD (Range)				
Age (year)	43.9 ± 10.8 (23-68)	47.8 ± 12.8 (23-68)	44.2 ± 14.3 (23-79)	43.5 ± 12.4 (23-72)	45.1 ± 13.2 (23-79)
Weight (kg)	71.3 ± 15.3 (47-112)	69.7 ± 15.5 (47-120)	67.4 ± 9.9 (43-87)	71.9 ± 15.9 (36-112)	69.6 ± 14.0 (36-120)
Height (cm)	168.2 ± 7.3 (152-183)	166.5 ± 6.6 (153-183)	165.4 ± 8.1 (145-178)	167.4 ± 9.5 (130-183)	166.4 ± 8.2 (130-183)
	N (%)				
Sex	41 Males (89.1%)	32 Males (84.2%)	35 Males (81.4%)	35 Males (83.3%)	102 Males (82.9%)
	5 Females (10.9%)	6 Females (15.8%)	8 Females (18.6%)	7 Females (16.7%)	21 Females (17.1%)

Subject Characteristics and Main Criteria for Inclusion:

Subjects were adult Japanese male and female volunteers 20 years of age or older with moderate to severe chronic plaque psoriasis. Females of childbearing potential were not pregnant or breast-feeding and were practicing an acceptable method of birth control throughout the study and for 150 days after the last study drug administration. Subject had moderate to severe chronic plaque psoriasis (psoriasis vulgaris) defined by ≥ 12 PASI score and $\geq 10\%$ BSA involvement at the screening and baseline visits. Subject had a clinical diagnosis of moderate to severe chronic plaque psoriasis for at least 6 months and had stable plaque psoriasis for at least 2 months before screening as determined by his/her medical records.



Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

	Adalimumab	Placebo
Dosage Form	Injectable Solution	Injectable Solution
Strength	40 mg in 0.8 mL	0 mg in 0.8 mL
Concentration	50 mg/mL	0 mg/mL
Mode of Administration	Subcutaneous	Subcutaneous
Lot No. /Product No.	23262HK/17102407	23263HK/17102496

Duration of Treatment: Approximately 24 weeks.

Methods of Evaluation

Pharmacokinetics:

Adalimumab serum concentrations were listed by subject and summary statistics were calculated by treatment group. Adalimumab serum concentrations below LOQ were treated as zero for the summary statistic calculations. In addition, plots comparing mean serum adalimumab trough concentrations by treatment group from this study (M04-688, Japanese subjects with psoriasis) and from Study M02-575 (Japanese subjects with RA) were prepared.

To test dose proportionality for Study M04-688, individual dose-normalized Week-24 adalimumab trough serum concentrations were compared across the three dose groups using analysis of variance (ANOVA).

Immunogenicity:

AAA concentrations were listed by subject. The percentage of subjects who were AAA+ was reported by treatment group. A subject was considered to be AAA+ if the subject had at least one AAA+ sample.

The impact of AAA on serum adalimumab concentrations and the potential effects of AAA on efficacy and safety were also analyzed by carrying out subgroup analyses (*i.e.*, comparing between AAA+ and AAA- subjects).

Comparison of immunogenicity in Japanese subjects with psoriasis (Study M04-688) and that in Japanese subjects with RA (Study M02-575) was carried out.

Population Pharmacokinetics:

Population pharmacokinetic analysis of the serum adalimumab concentrations was carried out to quantify potential differences in pharmacokinetics between Japanese subjects with psoriasis (Study M04-688) and Japanese subjects with RA (Study M02-575).

The population pharmacokinetic analyses were performed to estimate adalimumab apparent clearance (CL/F) and apparent volume of distribution (V/F). CL/F was the pharmacokinetic parameter of primary interest, and V/F was of secondary interest. Comparison of the post-hoc pharmacokinetic parameters between the two populations was carried out.

Population pharmacokinetic models were built using a non-linear mixed-effect population modeling approach with the NONMEM software (double precision, Version V, Level 1.1) and a NMTRAN pre-processor.



Results/Summary

Pharmacokinetic Results:

The mean steady-state trough concentrations for 40 mg eow with or without an 80 mg loading dose were similar to each other at approximately 4 µg/mL. With the 80 mg loading dose, adalimumab concentrations reached or exceeded the steady-state level as early as Week 2. Without the 80 mg loading dose, the concentrations approached the steady-state level by approximately Week 12. From Week 12 to Week 24, the concentrations increased further by about 20%.

The mean steady-state trough concentration for 80 mg eow was approximately 14 µg/mL, which was more than proportionally higher compared to 40 mg eow with or without an 80 mg loading dose. The concentrations approached the steady-state level by approximately Week 12. From Week 12 to Week 24, the concentrations increased further by about 10%.

Immunogenicity Results:

Eight subjects (8/38, 21.1%) in the 40 mg eow dose group, three subjects (3/43, 7.0%) in the 40 mg eow with an 80 mg loading dose group, and two subjects (2/42, 4.8%) in the 80 mg eow dose group had at least one AAA+ serum sample. These results indicate a decrease in immunogenicity rate as the adalimumab dose increased. The overall AAA+ rate across all three dose groups was 10.6% (13/123).

Distribution of AAA Concentrations:

The AAA concentrations were low to moderate (20 to 2000 ng/mL) for the majority of the AAA+ samples. Although the numbers of AAA+ samples were small for each dose group, overall there was a trend for a decrease in AAA concentrations when the dose of adalimumab increased.

Effect of AAA on Serum Adalimumab Concentrations:

For the small number of AAA+ subjects (N = 13), mean serum adalimumab trough concentrations started to decline between Week 2 and Week 4. The mean adalimumab trough concentrations for the AAA+ subjects were negligible after Week 8 for 40 mg eow with or without an 80 mg loading dose, and were negligible after Week 12 for the 80 mg eow dose group. The mean serum adalimumab trough concentrations in AAA- subjects remained relatively constant or were still gradually increasing after Week 12.

Dose Proportionality in All Subjects and in AAA- Subjects:

The ANOVA results show that individual dose-normalized trough concentrations at Week 24 from subjects treated with 40 mg eow with or without an 80 mg loading dose were comparable ($p = 0.4517$ for all subjects and $p = 0.1247$ for AAA- subjects only). However, the dose-normalized trough concentrations were statistically significantly different between the 80 mg eow dose group and 40 mg eow dose groups with or without loading ($p \leq 0.0053$ for all subjects and $p \leq 0.0313$ for AAA- subjects only).

The mean dose-normalized adalimumab trough concentration of the 80 mg eow group was approximately 60-70% higher than that from the pooled 40 mg eow group for all subjects. A similar trend was seen for AAA- subjects only.

Effect of AAA on Efficacy:

Although the numbers of AAA+ subjects were small for each dose group, overall the results show that AAA+ subjects had statistically significantly lower PASI 75, PASI 50 and PASI 90 response rates than AAA- subjects at both Week 16 and Week 24 ($p < 0.001$).



Overall, the results suggest that AAA development reduced the efficacy of adalimumab in Japanese subjects with psoriasis, consistent with the higher adalimumab clearance, and hence, reduced adalimumab exposure in the presence of AAA.

Effect of AAA on Safety:

There were no severe or serious AEs reported in the AAA+ group, and there were no events of malignancies or opportunistic infections in either AAA+ or AAA- subjects. The treatment-emergent AEs reported in AAA- subjects were mild to moderate in severity. AAA did not affect the tolerability to adalimumab and there were no indications of any clinically important differences in safety between adalimumab-treated subjects who developed AAA vs. those who did not, except that relatively more AAA+ subjects compared to AAA- subjects had treatment discontinuation due to aggravated psoriasis consistent with the reduced efficacy seen in AAA+ subjects.

Comparison of Japanese Subjects with RA and with Psoriasis:

Immunogenicity:

The incidence of immunogenicity to adalimumab in Japanese subjects with psoriasis was much lower than that in Japanese subjects with RA given the same treatment regimen.

Serum Adalimumab Concentrations:

When not stratified by AAA status, the Japanese psoriasis population treated with 40 mg eow with or without the loading had approximately 35% higher exposure to adalimumab at steady state compared to the Japanese RA population treated with 40 mg eow. For the 80 mg eow treatment, exposure to adalimumab in the Japanese psoriasis population was almost double that in the Japanese RA population. The higher exposure in the Japanese psoriasis population was due in part to the lower incidence of AAA observed in the Japanese psoriasis population compared to that in the Japanese RA population.

Once stratified by AAA status, the two populations had similar adalimumab serum concentration vs. time profiles for AAA- subjects treated with 40 mg eow without the loading. For the AAA- subjects treated with 80 mg eow, the exposure difference between the two populations was reduced from approximately 100% (*i.e.*, double) to about 57%.

For the AAA+ subjects, mean serum adalimumab trough concentrations started to decline between Week 2 and Week 4 in both Japanese RA and Japanese psoriasis subjects treated with 40 mg eow or 80 mg eow.

Population Pharmacokinetic Results:

The population pharmacokinetic analysis was carried out using the data from both the Japanese psoriasis and Japanese RA populations. The results showed that AAA was the most important single factor on CL/F. For AAA- subjects, the median weight-normalized CL/F value for Japanese psoriasis subjects was 42% lower than that for Japanese RA subjects. For AAA+ subjects, the median weight-normalized CL/F value for Japanese psoriasis subjects was 17% lower than that for Japanese RA subjects. When AAA+ and AAA- subjects were combined, the median weight-normalized CL/F value for Japanese psoriasis subjects was 58% lower than that for Japanese RA subjects, due in part to the lower immunogenicity rate observed in the Japanese psoriasis population than in the Japanese RA population. Weight-normalized V/F values were comparable between the two populations.



Conclusions:

In Japanese subjects with psoriasis, the mean steady-state trough adalimumab serum concentrations for the 40 mg eow dose groups with or without an 80 mg loading dose were similar to each other at approximately 4 µg/mL. The mean steady-state trough adalimumab serum concentration for the 80 mg eow dose group was approximately 14 µg/mL.

Eight subjects (8/38, 21.1%) in the 40 mg eow dose group, three subjects (3/43, 7.0%) in 40 mg eow with an 80 mg loading dose group, and two subjects (2/42, 4.8%) in the 80 mg eow dose group were AAA+. The overall AAA+ rate across all three dose groups was low at 10.6% (13/123).

Overall, the presence of AAA significantly reduced the exposure to adalimumab and the PASI response rates, although the numbers of AAA+ subjects were small for each dose group. AAA did not affect the tolerability to adalimumab and there were no indications of any clinically important differences in safety between adalimumab-treated subjects who developed AAA vs. those who did not, except that relatively more AAA+ subjects compared to AAA- subjects had treatment discontinuation due to aggravated psoriasis consistent with the reduced efficacy seen in AAA+ subjects.

Report Date: 11 July 2007