



2.0 Synopsis

Name of sponsor: Abbott Japan Co., Ltd. Eisai Co., Ltd.	Tabular format Applicable part of the dossier	(For national authority use only)
Name of finished product: (Humira / Rahira)	Volume no:	
Name of active ingredient: adalimumab (Genetical Recombination) (JAN)	Page:	
<p>Title of study: A Multicenter Open-Label Continuation Study of the Long-term Safety and Efficacy of Adalimumab (D2E7) in Japanese Subjects with Moderate to Severe Chronic Plaque Psoriasis</p> <p>Investigators: ██████████ 48 others.</p> <p>Publication(s): (N/A)</p> <p>Phase of development: 2/3</p> <p>Study period: Date of the first consent by the subject dosed with the study drug: April 5, 2006 (subject ID code: ██████████) Date of Week 28 visit of the last subjects dosed with the study drug: June 29, 2007 (subject ID code: ██████████)</p> <p>Objectives: ██████████ redacted information 23Sep2014</p> <p>The objectives of this study were to investigate the long-term safety and efficacy of two different dosage regimens (40mg eow and 80mg eow) of subcutaneously (sc) administered adalimumab every other week until approval of study drug in Japanese subjects with moderate to severe chronic plaque psoriasis (Ps) who have completed 24 weeks of Protocol M04-688 and received 28 weeks treatment with adalimumab in protocol M04-702. .</p> <p>This is a cumulative report based on an interim analysis which objectives were:</p> <ol style="list-style-type: none"> 1) to evaluate 52-week long-term safety and efficacy data of adalimumab 40 g eow and 80 mg eow; 2) to investigate the effect of dose escalation to 80 mg eow in non-responders (PASI below 50) in those patients on 40 mg eow; 3) to investigate pharmacokinetics of adalimumab and 4) to study anti- adalimumab antibodies. <p>Study method:</p> <p>This was a continuation trial of adalimumab in subjects with moderate to severe chronic plaque psoriasis who had completed study M04-688. The treatment of the study drugs was to be continued until the approval of this study drug for psoriasis indication in Japan. All study weeks in this protocol were given the 'x' designation to differentiate the M04-702 visits from the M04-688 visits.</p> <p>All subjects who had completed the observation and evaluation of Week 24 of the M04-688 study and had been randomized to active therapy continued to receive their previous dose of adalimumab (40 mg eow or 80 mg eow) in this extension study (M04-702). Subjects who were randomized to the placebo group in M04-688 were re-randomized to receive either 40 mg (without a single loading dose of 80 mg) or 80 mg eow adalimumab in the M04-702 study (see Table 1). The groups were designated as 40 mg/40 mg eow group, 40 mg (loading)/40 mg eow group, 80 mg/80 mg eow group, placebo/40 mg eow group and placebo/80 mg eow group. Week 24 (Week 0x in M04-702) non-responder were to be eligible for further treatment in M04-702 after the investigator evaluated the risk/benefit.</p> <p>Study medication was given in an open -label fashion using prefilled syringe for both treatment arms in M04-702 after the case report forms up to Week 16 in M04-688 had been collected and data had been cleaned. But when the collection and clean-up of clinical data up to Week 16 in M04-688 had not been completed by Week 0x in M04-702, blinded medication (either active treatment or placebo) using vials with same dose as in M04-688 was continued on subject basis to keep the blindness of study group in M04-688. At the latest, subjects were switched from blinded</p>		



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<p>treatment to open-label treatment by Week 8x in M04-702.</p> <p>Topical steroids of the class "strong", "medium" or "weak" (See protocol appendix 9 and 10), or vitamin D3 formulation (See protocol appendix 10) that had been administered as part of the M04-688 rescue treatment (applicable for the whole body) for non-responders needed to be tapered off and discontinued in M04-702 study within 2 weeks when open-label treatment had been started. Subjects were allowed to continue to use bland emollients throughout the entire study period. In addition, subject were allowed to continue to use "weak" or "medium" topical corticosteroids throughout the entire study period, however, when these treatments had been applied for the whole body during the rescue period (from Week 16 to Week 24) of M04-688, it was necessary to be tapered off (applicable area of the body should be limited again to the palms, soles, faces, scalp, and groin) within 2 weeks after treatment with prefilled syringe had been started.</p> <p>On or after Week 12x, subjects had been receiving 40mg eow of adalimumab (40 mg/40 mg eow group, 40 mg (loading)/40 mg eow group, placebo/40 mg eow group) and with a less than PASI 50 response from the baseline psoriasis area and severity index (PASI) score in M04-688 (non-responders), were to have the option to increase the dose to 80 mg eow of adalimumab based on the PASI score assessments at the scheduled visits at 4-week intervals between weeks 12x and 40x and at 12-week intervals after week 40x. But once the dose was escalated, the decrease of dose to 40 mg eow was not to be permitted. For non-responders treated with 80 mg eow (80 mg/80 mg eow group and placebo/80 mg eow group), the investigator was to evaluate the risk/benefit for further treatment of adalimumab.</p> <p>At Week 28x, all subjects who had been randomised to an 80 mg eow dose group (80 mg/80 mg eow group and placebo/80 mg eow group) at the beginning of M04-688 or M04-702 (from the placebo group in M04-688) was to be dosed down to 40 mg eow to continue the therapy. This mandatory dose reduction was not to be applied to subjects who were originally randomised to a 40 mg eow dose group and had been dosed up to 80 mg eow, because of no response to the treatment with 40 mg eow. After the dose reduction, it was to be allowed to dose up again to 80 mg eow when patients became non-responders to the treatment of 40 mg eow based on the PASI score assessment at the scheduled visit. But once the dose was escalated, the decrease of dose to 40 mg eow was not to be permitted. Subjects who had dosed up from 40 mg eow to 80 mg eow after Week 12x until Week 28x were to maintain the dose of 80 mg eow until the completion of this study (See section 9.2.6).</p> <p>Blood samples for pharmacokinetic analysis (serum adalimumab and AAA concentrations) were to be collected per subject prior to the administration at Week 8x, 16x, 28x, 40x and 52x, and every 12 weeks after Week 52x, the Study Completion/ Early Termination and the 28-day follow-up Visit. The data at Week 24 in M04-688 was used for the one at Week 0x in this study, and additional blood samples for Week 0x in M04-702 was not collected.</p> <p>Efficacy and safety measurements were to be performed throughout the study according to the Schedule of Assessments.</p> <p>A 28-days follow-up visit from Early termination of the study or the study completion and a final phone call or visit 70 days from the last administration of study drug were to be performed for all subjects who prematurely discontinued from the study or completed this study.</p> <p>Each subject was to receive either adalimumab 40 mg or 80 mg every other week throughout this extension study.</p>		
<p>Number of analysed subjects: Consented: 147 subjects, Received study treatment: 147 subjects, Completed: 112 subjects.</p>		



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A total of 147 subjects were analyzed for efficacy, pharmacokinetic, and safety assessment in this interim report.		
<p>Target disease: Subjects were adult Japanese men and women with moderate to severe chronic plaque psoriasis who met all of the inclusion criteria and none of the exclusion criteria.</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. All subjects who had completed study M04-688. 2. If female subject of childbearing potential, she was not considering becoming pregnant and practicing one of the following methods of birth control throughout this study and for 150 days after the last administration of study drug and the result of a urine pregnancy test, which was performed at each investigative site prior to the start of first dosing of this study, was negative: <ol style="list-style-type: none"> a. Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD) b. Oral contraceptives during/prior to study drug administration of M04-688 and throughout this study and for 150 days after the last study drug administration c. A vasectomized partner 3. Subject who could continuously receive isoniazide (INH) for the prophylaxis of latent TB infection if they had been receiving INH at M04-688 (INH must have been administered for 9 months from starting administration of the drug). 4. Subject had to be able and willing to provide written informed consent and comply with the requirements of this study protocol. <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Subject had other active skin diseases (e.g. urticaria, atopic dermatitis) or skin infections (bacterial, fungal, or viral) that may interfere with the evaluation of psoriasis, with the exception of footpad trichophytosis (athlete's foot). 2. Subject could not avoid topical therapies, "strong", "very strong" or "strongest" corticosteroids (Japanese classification) or vitamin D3 formulation etc. during the study. Subjects were allowed to use: <ol style="list-style-type: none"> a. Bland emollients, b. "weak" and "medium" class topical corticosteroids on the palms, soles, face, scalp and groin only. 3. Subject could not avoid UVB or UVA phototherapy, including topical or systemic PUVA and Geockerman therapy and Ingram therapy, during the study. 4. Subject could not avoid systemic therapies (cyclosporine, retinoids, methotrexate, tacrolimus, azathioprine, hydroxyurea, salazusulfapyridine, glucocorticoids etc.) during the study. 5. Subject planned to receive a live vaccine during the study. 6. Subject had developed a poorly controlled medical condition during M04-688, such as uncontrolled diabetes, unstable ischemic heart disease, congestive heart failure, recent cerebrovascular accidents, recent stroke, active inflammatory bowel disease, active peptic ulcer, and any other condition which, in the opinion of the investigator, would put the subject at risk by the continuation of the treatment with study drug. 7. Subject with a documented history of recurrent infections. 8. Subject had new onset of central nervous system (CNS) demyelinating disease during M04-688 study. 		



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9. Subject had new onset of cancer, lymphoma, leukemia or lymphoproliferative disease during M04-688 study.
10. Subject had new onset of listeriosis, histoplasmosis, active TB or persistent chronic or active infections requiring hospitalization during M04-688 study.
11. Subject had immune deficiency or was immunocompromised or immunosuppressed, or had started to treat with other immunosuppressive agents during M04-688 study.
12. Female subjects who were pregnant during M04-688 study or considered becoming pregnant during the study or for 150days after the last administration of study drug.
13. Subject had a clinically significant drug or alcohol abuse problem during M04-688 study.
14. Subject had new onset of erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or medication-exacerbated psoriasis during M04-688 study.
15. Subject had a definite diagnosis of systemic lupus erythematosus, scleroderma, or rheumatoid arthritis.
16. Subject was considered by the investigator, for any reason, to be an unsuitable candidate for the study.

Test Product, Dose/Strength/Concentration and Mode of Administration, Lot Number:
Test Product: Adalimumab (40 mg / 0.8mL) in prefilled syringe or vial for injection
Dose: adalimumab 40 mg or 80 mg
Mode of administration: subcutaneous administration
Lot Number:

<Prefilled syringe>

Study drug	Lot/product number	Production No.	Concentration of product	Date of manufacture	Expiration date
adalimumab (D2E7) 40 mg/0.8 mL		RT1A	50 mg/mL		
		RTXA	50 mg/mL		

<Vial>

Study drug	Lot/product number	Production No.	Concentration of product	Date of manufacture	Expiration date
adalimumab (D2E7) 40 mg/0.8 mL		RS8A	50 mg/mL		
Placebo 0.8 mL		RS8A	0 mg/mL		

Control drug: N/A

Study period:
Up to the approval of this study drug for psoriasis indication in Japan (2010 Jan).

Evaluation criteria

(1) Efficacy: The evaluations up to Week 28x were used for the analysis in this interim report.

- The proportion of subjects who achieved a clinical response defined by at least a PASI 50 response at Weeks 2x, 4x, 8x, 12x, 16x, 20x, 24x, 28x, 32x, 36x, 40x and 52x, and at every 12 weeks after Week 52x compared to baseline in M04-688.
- The proportion of subjects who achieved a clinical response defined by at least a PASI 75 response at Weeks 2x, 4x, 8x, 12x, 16x, 20x, 24x, 28x, 32x, 36x, 40x and 52x, and at every 12 weeks after Week 52x compared to baseline in M04-688.



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<ol style="list-style-type: none"> 3. The proportion of subjects who achieved a clinical response defined by at least a PASI 90 response at Weeks 2x, 4x, 8x, 12x, 16x, 20x, 24x, 28x, 32x, 36x, 40x and 52x, and at every 12 weeks after Week 52x compared to baseline in M04-688. 4. The duration of treatment success defined as the time from when 50% improvement in PASI was achieved compared to baseline in M04-688 to when 50% improvement in PASI was lost up to and including Week 12x. 5. The duration of treatment success defined as the time from when 50% improvement in PASI was achieved compared to baseline in M04-688 to when 50% improvement in PASI was lost up to and including Week 28x. 6. Proportion of subjects with a PGA score of "clear or minimal" at Weeks 2x, 4x, 8x, 12x, 16x, 20x, 24x, 28x, 32x, 36x, 40x and 52x, and at every 12 weeks after Week 52x. 7. Change from baseline values in Study M04-688 for DLQI and SF-36 at Weeks 16x, 28x, 40x and 52x, and at every 12 weeks after Week 52x. <p>(2) Safety variables:</p> <ol style="list-style-type: none"> a. The incidence of adverse events b. The incidence of SAEs c. The incidence of severe AEs d. The incidence of AEs resulted in the withdrawal of study drug e. Changes of laboratory data and vital signs from baseline of M04-688 <p>(3) Pharmacokinetic variables</p> <ol style="list-style-type: none"> a. Serum trough level of adalimumab b. Serum AAA level 		
<p>Statistical procedures:</p> <p>(1) Demographic and Baseline Characteristics: All demographic and other baseline characteristics were to be described with summary statistics.</p> <p>(2) Efficacy: Summary statistics were to be provided for all efficacy variables. The last evaluation prior to the first dose of study drug in study M04-688 was used as baseline. The evaluation after the first adalimumab treatment including M04-688 study was used to statistical analysis.</p> <p>(3) Safety: Adverse Event: Analysis of safety was to be performed in the Safety Analysis Set. Treatment-emergent adverse events were to be summarized. Treatment-emergent adverse event for the statistical analysis was used any adverse event with an onset date on or after the first dose of adalimumab (during m04-688 or m04-702 studies) up to last available information for subjects who completed week 28x visit or up to 70 days (5 x half life of the adalimumab dosing) after the last dose of study drug if subject discontinued prematurely from the study. The number and percent of subjects experiencing treatment emergent adverse event were to be tabulated by Medical Dictionary for Drug Regulatory Affairs (MedDRA) system organ class and MedDRA preferred term. In addition, a summary of adverse events by severity and relationship to study drug was to be presented. Treatment-emergent adverse events that were judged by the investigator to be probably or possibly related, and probably, possibly or probably not related to study drug were also to be tabulated. A</p>		



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<p>summary of serious adverse events, deaths, and adverse events leading to discontinuation were also to be provided. For subjects who had to continue placebo treatment upon entry into M04-702, AE reported after the first dose of placebo in M04-702 and before the first dose of adalimumab were to be listed separately. The evaluation after the first adalimumab treatment including M04-688 study was used to statistical analysis.</p> <p>Laboratory Data and Vital Signs: Mean change in laboratories variables and vital signs variables at each visit were to be summarized. The last evaluation prior to the first dose of adalimumab in study M04-688 or M04-702 was used as baseline. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 2 or higher were to be provided. Shift tables for change from baseline according to the normal range were also to be provided. The evaluation after the first adalimumab treatment including M04-688 study was used to statistical analysis.</p> <p>(4) Pharmacokinetics: Adalimumab concentration was to be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non-missing observations (n_{miss}), mean, median, standard deviation, coefficient of variation, minimum, and maximum. Mean concentration vs time plots by treatment group were to be provided. Serum AAA concentrations were to be listed by treatment group at each collection time.</p>		



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Summary - Conclusion

Efficacy:

Efficacy results of long-term administration of adalimumab (mean duration, 3.3 years) are described below:

- In OC-based tabulation, PASI 50, PASI 75 and PASI 90 response rates increased over time following the first dose of adalimumab. In Week 52 (ca. 1 year), Week 100 (ca. 2 years), Week 160 (ca. 3 years), and Week 208 (ca. 4 years), PASI 50 response rate was 95.6% (131/137 subjects), 95.4% (124/130 subjects), 100% (118/118 subjects), and 100% (43/43 subjects), respectively; PASI 75 response rate was 83.9% (115/137 subjects), 83.8% (109/130 subjects), 93.2% (110/118 subjects), and 93.0% (40/43 subjects), respectively; PASI 90 response rate was 70.1% (96/137 subjects), 69.2% (90/130 subjects), 76.3 (90/118 subjects), and 81.4% (35/43 subjects), respectively. These data indicated that high response rates were maintained for a long term following the first dose of adalimumab.
- All subjects in all treatment groups who achieved PASI 50 response by Week 12x, Week 28x, or study completion maintained PASI 50 response thereafter, indicating that the effect was maintained for a long time by continuous administration.
- Improvements in PGA, DLQI, and SF-36 were also maintained by administration of adalimumab.
- The results from subgroup analyses showed that the effectiveness of adalimumab was maintained regardless of the demographic characteristics, symptoms of psoriasis and previous treatment.
- It was demonstrated that the efficacy was obtained and maintained by dose escalation to 80 mg in subjects who were non-responders (<PASI 50) with adalimumab dose of 40 mg eow.
- When the subjects who had been receiving adalimumab 80 mg eow were transferred to 40 mg eow regimen, the efficacy slightly decreased after the dose reduction compared to that immediately before the dose reduction; however, the response rates generally remained stable from 1 year after the dose reduction onwards. Of the 147 subjects, 30 subjects who had a dose reduction tended to have heavier body weight (≥ 80 kg), longer duration of the disease, and a higher PASI score.
- In subjects who performed self-administration, there was no marked difference in the efficacy between before and after starting self-administration.



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<p>These results demonstrated that improvements in skin symptoms and QOL of subjects with psoriasis were maintained for a long time by adalimumab 40 mg eow or 80 mg eow. It was also shown that dose escalation to 80 mg eow was effective to obtain the efficacy for the subjects who had attenuated or insufficient efficacy under 40 mg eow treatment. Furthermore, administration of the reduced dose or self-administration did not have marked effects on the efficacy.</p> <p>Safety: The safety of long-term treatment with adalimumab is concluded as below.</p> <ul style="list-style-type: none">• A total of 2795 AEs occurred in 99.3% (146/147 subjects). AEs with an incidence of $\geq 10\%$ were nasopharyngitis, blood triglycerides increased, blood creatine phosphokinase increased, folliculitis, diarrhoea, alanine aminotransferase increased, antinuclear antibody increased, back pain, pharyngolaryngeal pain, headache, arthralgia, dental caries, blood uric acid increased, rhinorrhoea, upper respiratory tract infection, aspartate aminotransferase increased, injection site erythema, malaise, cough, eczema, pyrexia, insomnia, tinea pedis, hyperlipidaemia, adverse drug reaction, blood urine present, C-reactive protein increased, gamma-glutamyltransferase increased, pruritus, periodontitis, pain in extremity, and erythema. All these AEs which developed have been reported to have occurred up to 1 year after starting administration to date in previous clinical studies of adalimumab including Study M04-688, and no new AEs were observed due to prolongation of the treatment period up to 4 years (1553 days).• Incidence of AEs in each period (Weeks 0-26, Week 27-52, Weeks 53-78, Weeks 79-104, Weeks 105-130, Weeks 131-156, Weeks 157-182, Weeks 183-208, and Week 209 and thereafter) was 91.8%, 84.7%, 82.5%, 73.8%, 75.2%, 75.0%, 73.7%, 65.9%, and 52.4%, respectively, showing no increase in incidence of AEs due to extension of treatment period.• Of 2795 AEs which occurred after the first dose of adalimumab, 57.1% (1597 events) were judged as at least "probably not related" to the study drug, and 20.9% (585 events) were judged as at least "possibly related" to the study drug.• Most of all AEs or AEs that were judged as at least "probably related" to the study drug were mild.		



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<ul style="list-style-type: none"> • In the subjects who had a dose escalation to 80 mg, incidence of AEs did not increase after dose escalation (791.8 events/100 PY before the dose escalation, 454.1 events/100 PY after the dose escalation). All AEs which developed have been reported to date in previous clinical studies of adalimumab, and no new kind of AEs were noted. • In subjects who conducted self-administration, incidence of AEs did not increase after starting self-administration compared to that before starting self-administration (833.3 events/100 PY before starting and 464.5 events/100 PY). Any of the AEs which developed after starting self-administration has been reported to date in previous clinical studies of adalimumab. • There were no deaths. • A total of 40 SAEs were observed in 30/147 subjects (20.4%). Of these, 37 events in 27 subjects occurred during this study (Study M04-702), and 3 events in 3 subjects occurred during Study M04-688. SAEs by PT which were reported in at least 2 subjects were angina pectoris (3 subjects), cerebral infarction (2 subjects), and asthma (2 subjects). For causal relationship to the study drug, 3 events in 3 subjects were judged as "related," 11 events in 10 subjects as "probably related," and 8 events in 8 subjects as "not related." Fourteen events in 10 subjects were severe, 21 events in 18 subjects were moderate, and 5 events in 5 subjects were mild in severity. Eight subjects discontinued the study drug due to SAEs (██████ adenocarcinoma; ██████, pulmonary tuberculosis; ██████, acute myocardial infarction; ██████, angina pectoris; ██████, encephalitis; ██████ cerebral infarction; ██████, cervix carcinoma stage 0; ██████, cerebral infarction). Of 40 SAEs, 6 events were not resolved at the time of study completion. • A total of 24 AEs which led to discontinuation occurred in 17/147 subjects (11.6%) after the first dose of adalimumab. AEs by PT reported in at least 2 subjects which led to discontinuation were aggravation of psoriasis (3 subjects) and cerebral infarction (2 subjects). Of AEs leading to discontinuation, 4 events were still unresolved at the time of study completion (however, pulmonary tuberculosis in ██████ was judged as nearly resolved as of September 13, 2008). 		

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<ul style="list-style-type: none"> • A total of 708 infections were observed in 133/147 subjects (90.5%). AEs by PT with an incidence of $\geq 10\%$ were nasopharyngitis (76.9% [113 subjects]), folliculitis (23.8% [35 subjects]), dental caries (16.3% [24 subjects]), upper respiratory tract infection (15.6% [23 subjects]), and tinea pedis (12.2% [18 subjects]). Six events of serious infection occurred in 6 subjects. The clinical study was discontinued in 1 event in 1 subject, and administration of the study drug was temporarily interrupted in 53 events in 34 subjects; however, most of the infections could be managed without treatment or with other medications. • A total of 57 AEs of injection site reaction occurred in 34/147 subjects (23.1%). AE of injection site reaction by PT with an incidence of $\geq 10\%$ was injection site erythema in 13.6% (20 subjects) only. No SAEs of injection site reaction was observed. AEs of injection site reaction which led to discontinuation were observed in 2 subjects [redacted] injection site hypersensitivity; [redacted] injection site reaction). The majority of injection site reactions were mild and resolved either with no medication or with drug therapy. redacted information 23Sep2014 • A total of 156 hepatic events occurred in 67/147 subjects (45.6%). Hepatic events by PT with an incidence of $\geq 10\%$ were alanine aminotransferase increased (20.4% [30 subjects]), aspartate aminotransferase increased (14.3% [21 subjects]), and gamma-glutamyltransferase increased (10.9% [16 subjects]). Most of the events were mild and resolved without treatment. There was no increase or aggravation of hepatic events due to prolongation of treatment period. • Four events of malignancy (thyroid neoplasm, adenocarcinoma, cervix carcinoma stage 0, neoplasm) were observed in 4/147 subjects (2.7%), 1 event of opportunistic infection excluding tuberculosis (candidiasis) in 1/147 subject (0.7%), 1 event of tuberculosis (pulmonary tuberculosis) in 1/147 subjects, 1 event of lupus-like syndrome (cutaneous lupus erythematosus) in 1/147 subject (0.7%), and 1 event of cardiac failure congestive (pulmonary oedema) in 1/147 subject (0.7%). There were no demyelinating disease, allergic reaction or blood disorder. • Laboratory values and vital signs were all of no clinical concerns. <p>These results demonstrated that long-term 40 mg or 80 mg eow adalimumab subcutaneous injection is generally safe and excellent in tolerance. In addition, it has been confirmed that there are no safety problems in dose escalation from 40 mg eow to 80 mg eow and in self-administration. Pharmacokinetic results are described in the separate report (R&D/10/1218).</p>		



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Conclusion: Adalimumab was continuously administered to Japanese subjects with moderate to severe psoriasis with moderate to severe chronic plaque psoriasis who had completed a 24-week double-blind comparative study (Study M04-688) to assess the efficacy and safety of the long-term administration. As a result, it was demonstrated that the efficacy such as improvement of skin symptoms in psoriasis and of QOL noted after administration for 24 weeks were maintained over a long term. Furthermore, since neither an increase in incidence of AEs or occurrence of new AEs due to long-term continuous administration was observed, there were no safety problems about long-term continuous administration of adalimumab 40 mg or 80 mg, showing favorable tolerability. Dose escalation to 80 mg eow was effective to obtain the efficacy for the subjects who had attenuated or insufficient efficacy under 40 mg eow treatment, with no safety issues. Furthermore, it was confirmed that self-administration did not affect the efficacy or safety.		