



## 2.0 Synopsis

<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira		
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<b>Title of Study:</b> Open-Label Continuous Administration Study with Adalimumab (D2E7) in Subjects with Rheumatoid Arthritis		
<b>Investigator:</b> [REDACTED] total 64 personnel		
<b>Study Sites:</b> [REDACTED] Total 64 sites in Japan		
<b>Publications:</b> (N/A)		
<b>Studied Period (Years):</b> Aug 2004 to Feb 2009 First Subject First Visit: 12 Aug 2004 Last Subject Last Visit: 3 Feb 2009	<b>Phase of Development:</b> 2/3	
<b>Objectives:</b> The primary objective of the study is to assess the long-term safety of repeated subcutaneous administration of adalimumab in adult Japanese subjects with RA in an open-label study. The secondary objective is to determine efficacy in terms of magnitude and duration of maintenance of a 20%, 50%, and 70% improvement, based on the ACR response criteria (ACR20, ACR50 and ACR70; ACR 20/50/70) response after repeated subcutaneous administration of adalimumab.		

redacted information 14Nov2014



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira	<b>Page:</b>	
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<p><b>Methodology:</b></p> <p>This is an open-label continuation study including subjects who participated in the preceding dose-response study of adalimumab (M02-575 [redacted]). Subjects eligible to enter this study were as follows: subjects who completed the preceding dose-response study (referred to as M02-575 completers); subjects who had been shifted to the rescue arm (treated with disease-modifying anti-rheumatic drugs [DMARDs] except biological products, non-steroidal anti-inflammatory drugs [NSAIDs], and high doses of corticosteroids), but completed the 24-week preceding dose-response study (referred to as part of the M02-575 rescue arm). Prior to continuation into this study, consent from subjects to participate in this study was obtained and their eligibility was examined. M02-575 completers were subdivided into placebo, 20 mg, 40 mg, and 80 mg group, and all adalimumab group (including all of 20 mg, 40 mg, and 80 mg group) by DB dose in M02-575; those in the M02-575 rescue arm were subdivided into without DMARDs group and all DMARDs group, and the all DMARDs group were further subdivided into MTX group and other DMARDs group, by their concomitant medications.</p> <p>This study will continue until the approval of the study drug in Japan. During the study period, adverse events (AEs) are to be collected and the safety is to be evaluated on all of the subjects.</p> <p>This study was conducted at the same institutions where the preceding dose-response study was conducted. All the subjects initially received a subcutaneous (sc) dose of adalimumab 40 mg every-other-week (eow). Efficacy was evaluated with the ACR criteria at 4-week intervals through Week 24 and at 12-week intervals subsequently until the end of the study. If the subjects were assessed to be insufficiently responsive to the treatment [redacted] they were titrated to adalimumab 80 mg eow. However, if the subjects were rescued in the preceding study (treated with DMARDs, except biological products, with NSAIDs, and high dose of corticosteroids), they were not permitted to receive the increased dose of 80 mg, but continued to receive those concomitant medications such as DMARDs.</p> <p>Assessments of disease activity and laboratory tests (hematological, biochemical, and urinalysis) were performed at 4-week intervals through Week 24 and at 12-week intervals subsequently until the end of the study (or premature discontinuation). Clinical and safety assessments were performed at the follow-up investigation visit, 28 days after last dose (or premature discontinuation). Additionally, AEs were monitored up to 70 days (5 half-lives) after the last dose (or premature discontinuation) of study drug. Anti-nuclear antibodies (ANA) and anti-double stranded deoxyribonucleic acid (dsDNA) antibody by radioimmunoassay (RIA) were examined every 24 weeks (or premature discontinuation).</p> <p>The results in Week 24 of the preceding dose-response study were used for examination items at enrollment into the study, and the items without overlap (assessment of eligibility, chest X-ray and so on) were newly performed.</p>		

redacted information 14Nov2014



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b> <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira		
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<b>Number of Subjects (Planned and Analyzed):</b> Planned: 320 subjects (as maximum number), enrolled 312 subjects, completed 162 subjects. 309 subjects were included in the efficacy or safety analysis.		
<b>Diagnosis and Main Criteria for Inclusion:</b> Among the subjects who completed the preceding dose-response study, or the subjects who were rescued and completed the preceding 24-week study, those who consented to the continuation of study drug administration, met the inclusion criteria, and did not violate the exclusion criteria, were eligible for this study. <u>Inclusion criteria</u> <ol style="list-style-type: none"><li>1. Female subjects who were postmenopausal for at least 1 year or surgically sterile or practicing birth control throughout the study and for 90 days after the last administration of study drug.</li><li>2. All female subjects of childbearing potential who had a negative pregnancy test (serum) at Week 24.</li><li>3. Subjects who received isoniazid in the preceding dose-response study must have been able to continue receiving it (for at least 1 month after the start of receiving it).</li><li>4. Subjects must have been able and willing to provide written informed consent and to comply with the requirements of this study protocol.</li></ol> <u>Exclusion criteria</u> <ol style="list-style-type: none"><li>1. A subject who experienced an inflammatory joint disease other than RA during the period of the preceding dose-response study, such as mixed connective tissue disease, Rheumatoid factor (RF)-negative spondyloarthritis, psoriatic arthritis, Reiter's syndrome, systemic lupus erythematosus, progressive systemic sclerosis (scleroderma), and arthritis which occurred prior to the age of 16 years, but not including Sjögren's syndrome.</li><li>2. A subject who experienced any of the following during the preceding dose-response study:<ul style="list-style-type: none"><li>• Severe or uncontrollable diabetes</li><li>• A joint surgery (on the joint to be assessed in this study)</li></ul></li><li>3. A subject who planned to have joint surgery (on the joint to be assessed in this study).</li><li>4. A subject who received the prohibited concomitant medication(s) during the preceding dose-response study.</li></ol>		



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira	<b>Page:</b>	
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<p>5. A subject with a history of any of the following during the preceding dose-response study:</p> <ul style="list-style-type: none"> <li>• Drug or alcohol abuse</li> <li>• Intravenous drug abuse</li> <li>• Active infection with Listeria or tuberculosis</li> <li>• Lymphoma or leukemia</li> <li>• Malignancy (excluding basal cell carcinoma that was completely excised with no metastasis)</li> </ul> <p>6. A subject who received a live vaccine during the preceding dose-response study, or was to receive a live vaccine during the period of this study.</p> <p>7. A subject for whom the evidence of past tuberculosis (calcified node and pleural scar) was obtained on chest X-ray examination at screening.</p> <p>8. A subject who experienced the central nervous system (CNS) demyelinating disorders during the preceding dose-response study.</p> <p>9. A subject who became wheelchair-bound or bedridden (Class IV by the Classification of Functional Status in Rheumatoid Arthritis [redacted])</p> <p>10. A female subject who became pregnant or began to lactate during the preceding dose-response study.</p> <p>11. A subject whom the investigator considered ineligible for study participation</p>		
<p><b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b></p> <p>Test Product: Aqueous injection containing 50 mg/mL adalimumab (pre-filled syringe)</p> <p>Dose/Strength/concentration: 40 mg eow (the dosage could be increased to 80 mg eow in the subjects assessed to be insufficiently responsive to the treatment as defined in the protocol)</p> <p>Mode of administration: subcutaneous administration</p> <p>Lot number: [redacted]</p> <p><b>Duration of Treatment:</b></p> <p>Until marketing product (Humira) was available in each site.</p>		
<p><b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b></p> <p>N/A</p>		

redacted information 14Nov2014



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira		
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<b>Criteria for Evaluation</b> <b>Efficacy:</b> Safety Variables: <ul style="list-style-type: none"><li>· Primary Endpoint: During the study, ACR20, ACR50, and ACR70 response were evaluated every 4 weeks until Week 24 and every 12 weeks thereafter.</li></ul> Secondary Endpoints: <ul style="list-style-type: none"><li>· Individual component of ACR efficacy criteria and duration of morning stiffness.</li></ul> <b>Pharmacokinetic:</b> <ul style="list-style-type: none"><li>· Serum AAA and adalimumab concentrations.</li></ul> <b>Safety:</b> <ul style="list-style-type: none"><li>· Vital signs, physical examinations (including subjective symptoms), and laboratory values (hematology tests, blood chemistry tests, and urinalysis), were performed at 4-week intervals through Week 24 and at 12-week intervals subsequently.</li><li>· Chest x-ray and 12-lead ECG were performed every 24 weeks.</li><li>· Adverse events were collected from the time of informed consent and followed for 70 days after the last dose. Since this is an interim report, treatment-emergent AE was defined as AE that occurred between the first dose and 70 days post last study injection for the subjects who dropped from the study prior to Week 36, and between the first dose and the Week 36 visit for those subjects who are ongoing as of Week 36.</li></ul>		



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira	<b>Page:</b>	
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<p><b>Statistical Methods</b></p> <p><b>Efficacy:</b></p> <p>Descriptive statistics were calculated for full analysis set, and no hypothesis was tested. Since the number of subjects per single study institution was so small, site adjusted analysis was not planned.</p> <p>All efficacy measurements were summarized based on study visits; for the subjects who did not require rescue treatment during the M02-575 study, the baseline for all efficacy analyses were defined as the Week 0 of the M02-575 study; for the subjects who underwent rescue treatment in the M02-575 study, the baseline will be defined as the Week 0 of the M03-651 study. Efficacy endpoints were analyzed every 4 weeks until Week 24, and every 12 weeks thereafter.</p> <p>(1) ACR response rates (ACR20, ACR50 and ACR70) and relative ratio (%) of their components were calculated. Summary statistics (number of data, mean, 95% confidence intervals, standard deviation, the first semi-interquartile value, median, the third semi-interquartile value, minimum, and maximum) for each parameter of ACR was calculated.</p> <p>(2) For each parameter of ACR, mean of the changes and the changing rates from baseline.</p> <p>(3) Summary statistics (number of data, mean, 95% confidence intervals, standard deviation, the first semi-interquartile value, median, the third semi-interquartile value, minimum, and maximum) of duration of morning stiffness and changes from baseline.</p> <p><b>Pharmacokinetic:</b></p> <ol style="list-style-type: none"> <li>1. A listing of serum adalimumab concentration was to be provided.</li> <li>2. The percentage of subjects who are AAA positive was reported by treatment groups. Samples were considered to be AAA positive on treatment if the following criteria were met: the measured AAA concentration was &gt;20 ng/mL. [REDACTED]</li> </ol>		

redacted information 14Nov2014



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira		
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<b>Safety:</b> <p>All safety measurements were summarized based on adalimumab exposure; hence the last non-missing value prior to the first adalimumab injection were used as the baseline for all safety related analyses; for subjects who received adalimumab in the M02-575 study, baseline was defined as the last value prior to the first dose of adalimumab in the M02-575 study; for subjects who received placebo in the M02-575 study, baseline was defined as the last value prior to the first dose of adalimumab in this M03-651 study.</p> <p>(1) Exposure to Study Drug</p> <p>The number of injections planned and those performed were summarized with frequency and percentage. Summary statistics (mean and standard deviation) were calculated for the duration of study drug treatment.</p> <p>(2) Adverse Events</p> <p>Percentage of the subjects who had at least one adverse event of in the safety analysis set of subjects was calculated as frequency (%) of AEs. Frequency (%) of AEs by organ classified by MedDRA (version 10.1) System Organ Class (SOC), and by symptom/finding classified by MedDRA Preferred Term (PT) were also calculated.</p> <p>Summarization by intensity and relationship to study drug was performed. For serious AEs, and severe/life-threatening AEs, the details were described. A listing of all adverse events was prepared.</p> <p>(3) Laboratory Test Results and Vital Signs</p> <p>A listing of subjects with abnormal results (under or above the standards) was prepared. Summary statistics were calculated by visit. Summary statistics of the change from the initial state (before the first administration) were also calculated.</p>		



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira		
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<b>Summary/Conclusions</b> <b>Efficacy Results:</b> <ul style="list-style-type: none"><li>● ACR20 response rate for the FAS was 51.6% (157/304 subjects) at Week 4, 67.6% (163/241 subjects) at Week 36, 69.3% (158/228 subjects) at Week 48 (ca. 1 year), 75.8% (72/95 subjects) at Week 108 (ca. 2 years), 74.4% (61/82 subjects) at Week 156 (ca. 3 years), 88.9% (8/9 subjects) at Week 204 (ca. 4 years), and 54.2% (166/306 subjects) at the final evaluation.</li><li>● ACR50 response rate for the FAS was 24.3% (74/304 subjects) at Week 4, 41.1% (99/241 subjects) at Week 36, 43.4% (99/228 subjects) at Week 48 (ca. 1 year), 45.3% (43/95 subjects) at Week 108 (ca. 2 years), 57.3% (47/82 subjects) at Week 156 (ca. 3 years), 77.8% (7/9 subjects) at Week 204 (ca. 4 years), and 34.0% (104/306 subjects) at the final evaluation.</li><li>● ACR70 response rate for the FAS was 9.9% (30/304 subjects) at Week 4, 20.7% (50/241 subjects) at Week 36, 22.8% (52/228 subjects) at Week 48 (ca. 1 year), 28.4% (27/95 subjects) at Week 108 (ca. 2 years), 32.9% (27/82 subjects) at Week 156 (ca. 3 years), 44.4% (4/9 subjects) at Week 204 (ca. 4 years), and 19.0% (58/306 subjects) at the final evaluation.</li><li>● [Redacted]</li><li>● [Redacted]</li></ul>		

redacted information 14Nov2014





<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira		
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<ul style="list-style-type: none"><li>● Mean changes in individual ACR components (TJC, SJC, physician's global assessment of disease activity, subject's global assessment of disease activity, subject's assessment of pain, patient's assessment of physical disability, CRP) of the FAS showed a significant decrease at all evaluation weeks.</li></ul> <p>As shown above, 40 mg eow adalimumab administration was almost consistently effective for a long term (4 years or more at longest). For some subjects who experienced attenuation of efficacy with monotherapy with adalimumab, restoration of efficacy was observed after dose escalation to 80 mg eow.</p> <p><b>Pharmacokinetic Results:</b></p> <div data-bbox="297 953 1393 1247" style="background-color: black; width: 100%; height: 140px; margin: 10px 0;"></div> <p>Serum adalimumab concentration was lower in AAA positive subjects than in AAA negative subjects within any of the subject groups receiving adalimumab 40 mg eow alone, using concomitant MTX, or having escalated to 80 mg eow.</p>		

redacted information 14Nov2014



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira	<b>Page:</b>	
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<p><b>Safety Results:</b></p> <p>Safety results for Self-Injection Set 1 are follows;</p> <ul style="list-style-type: none"> <li>● In the safety analysis set, 96.8% (299/309) of the subjects experienced a total of 3497 AEs (667.9 events per 100 patient-years). Of the safety analysis set, the incidence of AEs in the subjects who were in the rescue arm in the dose-response study and used a DMARD in this study (88 subjects) was 97.7% (86/88 subjects) (731.3 events/100 patient-years). The incidence of AEs in those who used MTX (67 subjects) was 97.0% (65/67 subjects) (678.6 events/100 patient-years).</li> <li>● Adverse events with an incidence of <math>\geq 10\%</math> were nasopharyngitis (45.0%, 139/309 subjects), adverse drug reaction (23.6%, 73/309 subjects), DNA antibody positive (16.2%, 50/309 subjects), rheumatoid arthritis (aggravated) (15.2%, 47/309 subjects), constipation (13.6%, 42/309 subjects), rash and bronchitis (13.3%, 41/309 subjects each), insomnia (12.6%, 39/309 subjects), antinuclear antibody positive and contusion (12.3%, 38/309 subjects each), pruritus (12.0%, 37/309 subjects), upper respiratory tract infection (11.7%, 36/309 subjects), headache (11.0%, 34/309 subjects), and diarrhoea, injection site erythema, and eczema (10.0%, 31/309 subjects each).</li> <li>● AEs assessed as at least “probably not” related to the study drug were observed in 91.6% (283/309) of the subjects in the safety analysis set. AEs assessed as at least “possibly” related to the study drug were observed in 71.5% (221/309) of the subjects in the safety analysis set.</li> <li>● A total of 80 AEs which were severe in intensity occurred in 14.9% (46/309) of the subjects in the safety analysis set. Severe AEs which occurred in <math>\geq 2</math> subjects were rheumatoid arthritis (aggravated) (9 subjects), joint destruction (7 subjects), spinal compression fracture (3 subjects), and anaemia, pneumonia, pyelonephritis acute, cerebral infarction, tendon rupture, cerebral haemorrhage, and pleurisy (2 subjects each).</li> <li>● New AEs after dose escalation were observed in 83.0% (39/47) of the subjects. Serious AEs were seen in 25.5% (12/47) of the subjects, severe AEs in 21.3% (10/47), AEs leading to discontinuation in 12.8% (6/47), and AEs leading to death in 2.1% (1/47). One subject died after dose escalation. No noteworthy AEs occurred due to dose escalation.</li> <li>● Three subjects died during this study. Subject [REDACTED] died due to pneumonia staphylococcal (probably related) which occurred during suspension of the study drug. Subject [REDACTED] died of cerebral haemorrhage (probably not related) which occurred at 6 weeks after discontinuation of the study drug. Subject [REDACTED] died of lung abscess at 106 days after the final dosing of the study drug (not counted as an adverse event since it occurred more than 70 days after the final dosing of the study drug).</li> </ul>		

redacted information 14Nov2014



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> adalimumab (JAN)	<b>Page:</b>	
<ul style="list-style-type: none"> <li>● In this study, 35.9% (111/309) of the subjects in the safety analysis set had a total of 232 SAEs. SAEs with an incidence of <math>\geq 3\%</math> were rheumatoid arthritis (aggravated) (8.1%, 25/309 subjects) and joint destruction (3.9% , 12/309 subjects). Of the SAEs, there were a total of 42 AEs leading to discontinuation in 30 subjects, 71 AEs severe in intensity in 42 subjects, and 86 AEs at least “Probably” related to the study drug in 53 subjects.</li> <li>● A total of 64 AEs leading to discontinuation occurred in 16.5% (51/309) of the subjects in the safety analysis set. AE leading to discontinuation with an incidence of <math>\geq 3\%</math> was rheumatoid arthritis (aggravated) (4.2%, 13/309 subjects). AEs leading to discontinuation included 42 SAEs in 30 subjects, 22 severe AEs in 16 subjects, and 42 AEs at least “Probably” related to the study drug in 32 subjects.</li> <li>● Infectious diseases were seen in 72.5% (224/309) of the subjects in the safety analysis set. Infectious diseases with an incidence of <math>\geq 3\%</math> were nasopharyngitis (45.0%, 139/309 subjects), bronchitis (13.3%, 41/309 subjects), upper respiratory tract infection (11.7%, 36/309 subjects), pharyngitis (8.7%, 27/309 subjects), gastroenteritis and influenza (5.5%, 17/309 subjects each), cellulitis (4.5%, 14/309 subjects), herpes zoster, nail tinea, and tinea pedis (3.9%, 12/309 subjects each), and cystitis (3.6%, 11/309 subjects).</li> <li>● A total of 99 injection site reactions occurred in 20.4% (63/309) of the subjects. Injection site reactions with an incidence of <math>\geq 3\%</math> were injection site erythema (10.0%, 31/309 subjects), injection site reaction (8.1%, 25/309 subjects), and injection site pruritus (4.5%, 14/309 subjects).</li> <li>● A total of 71 events of hepatic dysfunction occurred in 14.6% (45/309) of the subjects. Excluding severe hepatic enzyme increased in Subject # [REDACTED] all the other events were mild in intensity.</li> <li>● There were 5 event of malignant (skin neoplasm, Hodgikin's disease, large intestine carcinoma, cervix carcinoma, and gastric cancer) in 1.3% (4/309 subjects).</li> <li>● A total of 9 events of opportunistic infection occurred in 2.3% (7/309) of the subjects, consisting of 7 events of oral candidiasis in 5 subjects, 1 event of candidiasis in 1 subject, and 1 event of cryptococcosis in 1 subject.</li> <li>● Two events of TB occurred in 2 subjects.</li> <li>● No clinically relevant issues were noted for laboratory values or vital signs.</li> </ul>		

redacted information 14Nov2014



<b>Abbott Laboratories</b> Abbott Japan Co., Ltd. Eisai Co., Ltd.	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Humira		
<b>Name of Active Ingredient:</b> adalimumab (JAN)		
<b>Conclusions:</b> <p>An open-label continuation study of adalimumab was conducted in Japanese adult patients with RA who had completed the preceding dose-response study or who were transferred to the rescue arm in the preceding dose-response study and stayed for 24 weeks after initiation of the study drug administration, and the safety, efficacy, and pharmacokinetics of the long-term repeated subcutaneous administration (up to 4 years) were investigated. No marked changes from the preceding dose-response study were observed in adverse events and their incidences, and there were no noteworthy physical findings or no abnormalities in vital signs and laboratory values, demonstrating the overall safety and favorable tolerability of long-term repeated subcutaneous dosing. It was also confirmed that the efficacy was maintained by the long-term repeated subcutaneous dosing. Pharmacokinetics revealed no inconsistency with the results obtained from Japanese and overseas clinical trials.</p>		