



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		
Title of Study: A Multi-center Open-Label Continuation Study with Subcutaneous D2E7 for Patients with Rheumatoid Arthritis Who Completed a Preceding Clinical Study with D2E7		
Investigator: Prof Dr Piet LCM van Riel, University Hospital Nijmegen, Department of Rheumatology, Geert Grooteplein 8, 6525 GA Nijmegen, The Netherlands		
Study Sites: 55 sites in Europe, Australia, and Canada		
Publications: None		
Studied Period (Years): First Subject First Visit: 19 Jun 2000 Last Subject Last Visit: 08 Jun 2006	Phase of Development: 3	
Objectives: <p>To investigate the clinical efficacy and safety of adalimumab given long-term to subjects with rheumatoid arthritis (RA). Subjects who completed a preceding trial with adalimumab were eligible for this open-label continuation study, in which they were offered adalimumab for another 3 years. Thereafter, the individual treatment period for each subject was extended so that subjects could receive at least 5 years of open-label treatment with adalimumab in Study DE018. Safety was evaluated by monitoring adverse events (AEs) and changes in clinical laboratory parameters and vital signs. The long-term efficacy of adalimumab was assessed by evaluating its effects on: (1) the signs and symptoms of RA; (2) physical function; (3) rates of clinical remission; and (4) patient-reported outcome (PRO) measures.</p> <p>The pharmacokinetic objective was to evaluate the individual adalimumab concentration data in 184 subjects whose adalimumab dose changed from 40 mg every other week (eow) to 40 mg weekly. This clinical study report focuses on the safety and efficacy assessments performed in the study.</p>		
Methodology: This was a multicenter, open-label continuation study involving subjects with RA (as defined by the 1987-revised American College of Rheumatology [ACR] criteria). Subjects who had previously completed a Phase 1, 2, or 3 adalimumab study in Europe, Australia, or Canada (<i>i.e.</i> , Studies DE001, DE003, DE004, DE007, DE010, or DE011) were able to roll over into Study DE018, in which they were		



offered adalimumab for an additional 3 years, equivalent to a total of 144 weeks of treatment. Thereafter, the individual treatment period of each subject was extended in order to achieve at least 5 years of open-label treatment with adalimumab in Study DE018. The open-label treatment period for each subject had been extended to at least 10 years of treatment with open-label adalimumab before being subsequently reduced to at least 5 years. For this reason, some subjects who participated in Study DE018 received open-label adalimumab for more than 5 years. Subjects who were exposed beyond 5 years terminated Study DE018 at the next possible scheduled study visit, but not later than 30 Jun 2006.

Subjects who were treated with methotrexate (MTX) in any of the prior feeder studies continued taking MTX at the oral dose they were receiving upon entry into Study DE018. Subjects could taper off corticosteroids, non-steroidal anti-inflammatory drugs, and MTX (preferred order) once they received adalimumab within Study DE018 for at least 4 months.

Subjects were screened for study eligibility at the Study Entry Visit (Visit [Week 0; Baseline] in Study DE018), based on the inclusion/exclusion criteria. A screening log was maintained that listed each subject who had signed an informed consent for the study. The reason was recorded for subjects who did not qualify, or for other reasons, did not enter the study.

Following study entry, subjects were examined every 8 weeks for 3 years (144 weeks). After 3 years, study visits occurred every 12 weeks. Subjects exposed to open-label adalimumab for more than 5 years were to have had study visits performed every 16 weeks until the subject achieved between 5 and 10 years of open-label treatment.

Subjects who completed the study after at least 5 years of open-label treatment in Study DE018 and planned to continue treatment with adalimumab were contacted by study site personnel within 70 days of the last dose of study drug to determine the occurrence of any AEs.

Subjects who prematurely withdrew from the study and subjects who completed at least 5 years of open-label treatment in Study DE018, but were not continuing treatment with adalimumab for any reason, were contacted by study site personnel 70 days after the last adalimumab injection to evaluate the occurrence of new AEs and to follow-up any ongoing AEs and serious adverse events (SAEs).

The long-term efficacy of adalimumab was measured using several assessments of disease activity including ACR response, European League Against Rheumatism (EULAR) response, tender joint count (TJC), swollen joint count (SJC), Physician Global Assessment of Disease Activity, Patient Global Assessment of Disease Activity, Patient Assessment of Pain, presence and duration of morning stiffness, C-reactive protein (CRP) and rheumatoid factor (RF) levels, erythrocyte sedimentation rate (ESR), Disability Index of the Health Assessment Questionnaire (HAQ-DI) score and HAQ-DI response (assessment of improvement in physical function), clinical remission as measured by the DAS28 (disease Activity Score) based on CRP and ESR, assessment of major clinical response (based on the ACR70 response), and the PRO measure Short Form-36 (SF-36) Health Status Survey. Safety was assessed on the basis of AEs and changes in clinical laboratory parameters (chemistry and hematology) and vital signs (heart rate and blood pressure).

Blood samples for the determination of adalimumab in serum were optional. Blood samples were collected at study entry (prior to dosing in Study DE018) and every 2 months (8 weeks) up to 24 months (96 weeks) and at the end of 3 and 6 month-post study visits.

Blood samples for the determination of serum anti-adalimumab antibodies (AAA) were collected by venipuncture in 15 ml vacutainer tubes with no anticoagulant. Blood samples were collected at study



entry (prior to dosing in Study DE018) and every 2 months (8 weeks) up to 24 months (96 weeks) and at the 3 and 6 month post study visits.
Number of Subjects (Planned and Analyzed): A total of 900 subjects were planned; 794 subjects were enrolled and analyzed.
Diagnosis and Main Criteria for Inclusion: Eligibility to enroll in Study DE018 required subjects to have completed a previous adalimumab study, and women of childbearing age had to have had a pregnancy test (urinary) and using a reliable method of contraception. All subjects had to be able and willing to give written informed consent and to comply with the requirements of the study protocol. Subjects could not have been formerly enrolled in Study DE018.
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: All subject received open-label adalimumab, which was administered as a 40 mg subcutaneous (SC) injection (0.8 mL/injection or 1.6 mL/injection) eow. The dosing frequency was to be increased to adalimumab 40 mg weekly in response to an increase in disease activity. All subjects received 40 mg of adalimumab as a total dose per injection. Multiple lot numbers were used. A by-subject listing of lot number is provided in Appendix 16.1__6 of the report.
Duration of Treatment: At least 5 years.
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: None
Criteria for Evaluation Efficacy: <u>Assessments for Signs and Symptoms of RA</u> ACR20/50/70/100 and EULAR Response, their components, along with CRP and RF were examined to assess the long-term efficacy of adalimumab in maintaining a reduction in the signs and symptoms of RA. ACR20/50/70/100: A subject was considered an ACR20/50/70/100 responder if the following three criteria were met: ≥ 20% (or ≥ 50, 70, or 100%) improvement in TJC, and ≥ 20% (or ≥ 50, 70, or 100%) improvement in SJC, and ≥ 20% (or ≥ 50, 70, or 100%) improvement in 3 of following 5: Patient Assessment of Pain Patient Global Assessment of Disease Activity Physician Global Assessment of Disease Activity HAQ-DI Acute phase reactant (CRP) An improvement at a particular visit of ≥ 20% was defined as a percent change from Baseline -20. The percent change was calculated by $100 \times (\text{Value} - \text{Baseline})/\text{Baseline}$. If the percent change in TJC



or SJC was not missing and percent change in at least three out of the remaining five ACR components was present, then the ACR20 response was calculated. If 20% improvement criteria were not met as specified above (*i.e.*, an ACR20 score could be calculated, but a 20% response was not achieved), then the ACR20 score was considered as "non-responder." If the percent change in TJC or SJC was missing, then the ACR20 response was considered as "missing." If the percent change in TJC or SJC was not missing and percent change in at least three out of the remaining five ACR components was missing, then the ACR20 response was considered as "missing."

The percent improvement of the different items was assessed at each visit compared to Baseline and rounded to 0.1%. In this study, CRP values were used as "acute-phase reactant" for calculation of ACR20.

EULAR Response: Good EULAR response [yes, no] or at least moderate EULAR response [yes, no] based on the EULAR response criteria using DAS28 based on CRP, as defined below:

DAS28 at current visit	Change in DAS28 From Baseline ^a		
	≤ -1.2	-1.2 to 0.6	≥ -0.6
≤ 3.2	Good	Moderate	None
> 3.2 to ≤ 5.1	Moderate	Moderate	None
> 5.1	Moderate	None	None

a. Baseline values were those prior to the first dose of study drug (either adalimumab or placebo) in the respective lead-in study.

TJC: An assessment of 28 joints (68 joints or regions for Studies DE007 and DE011) was done by pressure or joint manipulation on physical examination.

SJC: An assessment of 28 joints (66 joints or regions for Studies DE007 and DE011) was done by physical examination. The joints examined for swelling were the same as those examined for tenderness, except the hip joints were excluded.

Patient Assessment of Pain: An assessment of the subject's level of pain within the last 24 hours before the evaluation was made, using a 100 mm horizontal visual analogue scale (VAS). The left end of the VAS (0 mm) was for no pain and the right end of the VAS (100 mm) was for unbearable pain.

Patient Global Assessment of Disease Activity: The subject's overall assessment of arthritic activity within the last 24 hours (prior to the evaluation) was made, using a 100 mm horizontal VAS. The left end of the VAS (0 mm) indicated absence of symptoms and the right end of the VAS (100 mm) indicated very strong disease activity.

Physician Global Assessment of Disease Activity: An assessment of the subject's current disease activity was made by the physician using a 100 mm horizontal VAS. The left end of the VAS (0 mm) indicated absence of disease activity and the right end of the VAS (100 mm) indicated extreme disease activity.

Duration/Presence of Morning Stiffness: Duration of morning stiffness was measured in minutes; the presence of morning stiffness was a categorical variable (yes/no). Morning stiffness was not assessed in Study DE007.

CRP: A laboratory measure for evaluation of the acute-phase reactant.

ESR: A laboratory measure for evaluation of the acute-phase reactant.



RF: A laboratory measure (immunoglobulin) for the evaluation of RA.

Assessments for Improvement in Physical Function

HAQ-DI was examined to assess the long-term efficacy of adalimumab in maintaining improvement in physical function.

HAQ-DI: The HAQ-DI is a measure of disability that has a range from 0 to 3 with a higher score indicating a greater extent of functional limitations. The subject was to assess his/her physical function during the past week by measuring his/her ability to perform the following: (1) dress/groom; (2) arise; (3) eat; (4) walk; (5) reach; (6) grip; (7) maintain hygiene; and (8) maintain daily activity.

HAQ-DI Response: Subjects were classified as a "responder" if an improvement of 0.22; the minimally clinically important difference was achieved. The analysis was repeated defining "responder" as an improvement of 0.50, 0.75, and 1.00.

Assessments for Clinical Remission

The following variables were examined to assess the long-term efficacy of adalimumab in maintaining rates of clinical remission: clinical remission itself and major clinical response.

Clinical Remission: Clinical remission was assessed using the following criteria based on CRP.

DAS28 Score: Proportion of subjects who met the pre-defined DAS28 criteria of clinical remission (*i.e.*, DAS28 <2.6) based on CRP where $DAS28 = 0.56 * \sqrt{TJC28} + 0.28 * \sqrt{SJC28} + 0.36 * \log(CRP * 10 + 1) + 0.014 * (\text{Patient Global Assessment of Disease Activity}) + 0.96$

Clinical remission was also measured based on ESR. The same criteria applied with the exception of the DAS28 which was determined as the proportion of subjects who met the pre-defined DAS28 criteria of clinical remission (*i.e.*, DAS28 <2.6) based on ESR where $DAS28 = 0.555 * \sqrt{TJC28} + 0.284 * \sqrt{SJC28} + 0.70 * \ln(ESR [mm/1h]) + 0.0142 * (\text{Patient Global Assessment of Disease Activity})$.

Major Clinical Response: Subjects who maintained an ACR70 response for at least 6 months following the first injection of adalimumab.

Assessments for Improvement in Patient-reported Quality of Life

The SF-36 was examined to assess the long-term efficacy of adalimumab in maintaining improvement in patient-reported quality of life.

The SF-36 assesses: (1) limitations in physical functioning because of health problems; (2) limitations in usual role because of physical health problems; (3) bodily pain; (4) general health perceptions; (5) vitality; (6) limitations in social functioning because of physical or emotional problems; (7) limitations in usual role because of emotional problems; and (8) general mental health. In addition to these eight components, physical and mental component summaries were also derived using the following steps. First, the eight SF-36 scales were standardized using means and standard deviations from the general US population. Second, they were aggregated using weights (factor score coefficients) from the general US population. Finally, aggregate physical and mental component summary scores were standardized using a linear T-score transformation to have a mean of 50 and a standard deviation of 10 in the general US population.

Safety:

Safety assessments included AE assessment, physical exam results, vital sign measurements, and clinical laboratory results.



Statistical Methods:

Analyses of clinical assessment were carried out in the Full Analysis Set as well as for other sets or subgroups. Appropriate stratification for studies and centers were done. The data from former studies *e.g.*, Studies DE001/DE003, DE004, DE007, DE010 and DE011, respectively, were included in the analysis as well. Demographic and Baseline variables were done descriptively.

Efficacy:

The analysis of efficacy was done descriptively. All subjects who received at least one dose of study medication were included irrespective of possible protocol deviations. No confirmatory analysis was done. The analysis focused mainly on the maintenance of efficacy. Both the Baseline visit and the last visit of the original study were included in the analysis. All efficacy variables were described per visit and treatment received (statistical characteristics, frequency and percentage, confidence intervals). In order to assess a possible bias caused by dropouts, different approaches were used, *e.g.* all observed, LOCF, and completers only. In order to assess possible study or center effects, by-study and by-center tables were done for the most important efficacy parameters.

The analysis of dropouts vs. subjects continuing in Study DE018 per year for ACR20 response was added after database lock to the analyses described in the statistical analysis plan.

Pharmacokinetics:

Measurement of serum adalimumab and AAA concentrations were performed. Individual serum adalimumab concentrations were listed by visit times as defined in the protocol and summarized with appropriate descriptive summary statistics. Adalimumab concentrations in serum from Study DE018 were analyzed using a validated double antigen immunoassay. The lower limit of quantitation (LLOQ) for adalimumab was established at 2.5 ng/mL in diluted serum or 25 ng/mL in undiluted serum.

Serum AAA concentrations were listed at each collection time. The serum concentration of adalimumab at the corresponding collection time was also presented. The number of subjects with at least one AAA sample was reported.

Serum samples were analyzed for AAA using a validated double antigen immunoassay. The assay detects antibodies directed against epitopes on the entire adalimumab molecule. The lower limit of quantitation for samples analyzed for AAA was established at 0.5 ng/mL in diluted serum. For those samples with a quantifiable AAA concentration (above 5 ng/mL), additional suppression tests (addition of human serum) were performed to evaluate the specificity of the AAA response. The assay detects free (unbound) AAA. Adalimumab present in the sample complexes AAAs and prevents them from binding simultaneously to the capture- and detector-adalimumab. Samples containing measurable amounts of adalimumab may result in negative or borderline AAA results. Therefore, only samples in which the adalimumab concentration was low ($< 2 \mu\text{g/mL}$) were to be selected for AAA analyses. Serum samples were considered to be positive for AAA for this study if the following criteria were met:

- The measured AAA concentration was greater than 20 ng/mL;
- The signal was not reduced by 50% or more by addition of 10% human serum; and
- The sample for AAA was collected within 30 days after an adalimumab dose.



Plots of serum adalimumab and AAA concentrations from Study DE018 were generated.

Safety:

All subjects who received at least one injection of adalimumab were included in the safety analysis. Adverse events were presented by frequency and percentage. In addition, AEs of special interest, *e.g.*, SAEs, or AEs leading to premature study discontinuation, were listed and narratives are provided. Vital signs and laboratory data were described by statistical characteristics and frequency of abnormal values. The frequency of abnormal laboratory values was presented based on normal ranges.

Summary/Conclusions

Efficacy Results:

Efficacy was measured from the date of the first injection in Study DE018 onwards. Baseline for efficacy was the last non-missing observation before the first dose of study medication (adalimumab or placebo) in the respective feeder study.

The efficacy results from this open-label continuation study demonstrate that long-term administration of adalimumab results in: (1) maintained reduction of the signs and symptoms of RA; (2) maintained improvement in physical function; (3) maintained rates of clinical remission; and (4) maintained improvement in patient-reported quality of life. The demonstration of adalimumab efficacy following long-term administration is particularly clinically meaningful since it has been done in a subject population with advanced RA (mean duration of 144.1 months at the outset of the study).

Assessments for Signs and Symptoms of RA

ACR20/50/70/100 response rates demonstrate that the reductions in the signs and symptoms of RA achieved following 1 year of adalimumab exposure are sustained through 5 years of exposure relative to Baseline (Week 0) response rates.

An analysis was performed to compare the proportion of ACR20 responders who dropped out during each year *vs.* subjects who completed each year of study for five years. A substantial number of subjects, ranging from 28.5% at Year 1 to 66.7% at Year 5, were ACR20 responders when they dropped out of the study. These results are consistent with the reason for the discontinuation data, which showed that approximately one-fifth of the total number of subjects (171 subjects; 21.5% of the group) dropped out due to lack of efficacy over ≥ 5 years. The percentages were based on the total number of subjects (794) in the Intent-to-treat Analysis Set with 394 subjects who were treated with adalimumab for 60 to < 72 months and six subjects who received 72 to <84 months of treatment. Since substantial numbers of subjects who dropped out were ACR20 responders, conclusions based on the subjects who remained in Study DE018 are not biased in terms of efficacy. This analysis is consistent with the ACR response analysis and support the conclusion that ACR20 response is maintained with continued adalimumab through at least five years.

Results from the other efficacy measurements assessed in this study (EULAR response rates based on CRP and ESR, TJC68 and TJC28, SJC66 and SJC28, Patient Assessment of Pain, Patient Global Assessment of Disease Activity, Physician Global Assessment of Disease Activity, Duration/Presence of Morning Stiffness, and CRP, ESR, and RF levels) support the conclusion that the reductions in the signs and symptoms of RA achieved following 1 year of adalimumab exposure are sustained through 5 years of exposure.



Assessments for Improvement in Physical Function

Mean change from Baseline in HAQ-DI scores was maintained through 5 years of exposure to adalimumab. Clinically meaningful improvement (HAQ-DI change from Baseline ≤ -0.22) was seen at every timepoint.

The increased proportion of HAQ 0.22, HAQ 0.5, 0.75, and 1.0 responders was maintained through 5 years of exposure to adalimumab.

Results from other efficacy measurements assessed in this study (HAQ 0.22/0.50/0.75/1.0 response rates) provide supportive evidence that the improvements in physical function achieved following 1 year of adalimumab exposure are maintained through 5 years of exposure.

Assessments for Clinical Remission

The rate of clinical remission, as assessed by the DAS28 based on CRP and ESR, achieved following 1 year of adalimumab exposure was sustained through 5 years of exposure. Significant improvement, as defined by a change from Baseline of ≤ -1.08 , was seen at all timepoints.

Over the 5-year period of adalimumab treatment, a total of 203 of 786 subjects (25.8%) achieved a major clinical response.

Assessments for Improvement in Patient-Reported Quality of Life

Each individual domain and both summary component scores of the SF-36 demonstrated clinically meaningful improvements that were sustained at each timepoint through 5 years of adalimumab exposure. One exception was the emotional role domain, which maintained a clinically meaningful improvement through 4 years, but decreased at 5 years. Positive mean changes from Baseline in Z scores for all SF-36 domain scores also indicated improvement in quality of life.

Subjects With Dose Increase to Weekly

An additional set of analyses, ACR responses rates, TJC28, SJC28, and HAQ-DI score were performed on subjects who underwent a dose increase from eow to weekly. Subjects who switched from eow dosing to weekly dosing showed improvement in ACR20/50/70 response rates, TJC28, SJC28, and HAQ-DI scores. The improvement occurred at 8 weeks post-increase and was maintained to 16 weeks post-increase.

Pharmacokinetic Results:

Pharmacokinetic data and results are presented in a separate study report (R&D/06/542).

Safety Results:

Safety results obtained during Study DE018 demonstrate that 40 mg adalimumab when administered long-term is generally safe and well tolerated, regardless of whether adalimumab is administered as an eow SC injection or more frequently at weekly dosing intervals.

Adalimumab was generally safe and well tolerated following long-term administration as evaluated by the incidence of AEs overall, severe AEs, and drug-related AEs.

- A total of 782 subjects (98.5%) reported at least one treatment-emergent AE during the study. The most common AEs were RA (41.6%) and nasopharyngitis (36.0%); other common AEs reported by approximately 20% of subjects included cough, back pain, diarrhea, influenza, arthralgia, and headache. No notable difference in the incidence of severe AEs was observed based on adalimumab treatment received (eow or weekly).



- No new or unexpected trends in AE incidence were observed following long-term exposure to 40 mg adalimumab (all doses) based on sex, age, or body weight. The trends in AE incidence observed among subgroups based on corticosteroid use, RA disease status, and duration of RA at Baseline were characteristic of a middle-aged subject population with severe, long-term RA.
- A total of 515 subjects (64.9%) reported severe treatment-emergent AEs (*i.e.*, severe or life threatening/intractable). The most common severe AE was RA (11.3%).
- There were 662 subjects (83.4%) who reported treatment-emergent AEs considered by the Investigator to be at least possibly drug-related (*i.e.*, possibly, probably, or definitely related to study drug).

Adalimumab was generally safe and well tolerated following long-term administration as evaluated by the incidence of deaths, SAEs, permanent discontinuations due to AEs, AEs leading to dose reductions, and AEs that resulted in a temporary interruption of study drug.

- Thirteen deaths were reported during the study.
- There were 493 subjects (62.1%) who reported treatment-emergent SAEs. The most common SAEs were RA (8.9%) and osteoarthritis (6.2%).
- A total of 166 subjects (20.9%) permanently withdrew study drug due to treatment-emergent AEs. The most common AEs leading to withdrawal of study drug were RA (3.9%) and bacterial arthritis (1.0%).
- Sixteen subjects (2.0%) reported treatment-emergent AEs that resulted in a dose reduction. The most common AE leading to a dose reduction was RA (0.6%).
- A total of 453 subjects (57.1%) reported treatment-emergent AEs that resulted in a temporary interruption in study drug. The most common AEs resulting in a temporary interruption in study drug included nasopharyngitis, (5.4%), osteoarthritis (4.8%), bronchitis (3.9%), and influenza (3.5%).

Adalimumab was generally safe and well tolerated following long-term administration as evaluated by TNF inhibitor-related and other special AEs of interest.

- A total of 649 subjects (81.7%) reported treatment-emergent infectious AEs. The most common infectious AEs were nasopharyngitis (36.0%), bronchitis (16.4%), influenza (19.0%), urinary tract infection (15.1%), upper respiratory tract infection (14.6%), sinusitis (12.0%), and rhinitis (10.2%).
- A total of 131 subjects (16.5%) reported treatment-emergent serious infectious AEs. The most common serious infectious AEs were bacterial arthritis (2.1%) and pneumonia (2.1%). Four subjects died as a result of a serious infections (lung abscess and empyema; bilateral pneumonia; diverticulitis and sepsis; and multiple abscesses, sepsis, and acute septic myocarditis). Three of these four subjects had serious infections that were considered to be at least possibly related to adalimumab treatment.
- Thirty-five subjects (4.4%) reported treatment-emergent malignant AEs excluding non-melanoma skin cancers. The most common malignancies excluding non-melanoma skin cancers were breast cancer (0.8%) and neoplasm (0.6%). Three subjects died due to malignancies (cerebral tumor; adenoma-carcinoma of the duodenum (bulbus) with cholestasis and elevated liver enzymes; and adenocarcinoma). All three malignancies were considered to be treatment-related.



- Fifteen subjects (1.9%) reported treatment-emergent non-melanoma skin cancers. Thirteen (13) subjects had basal cell carcinoma and two subjects had a squamous cell carcinoma.
- A total of 49 subjects (6.2%) reported treatment-emergent AEs associated with immunologic reactions. The most common immunologic reactions were seasonal allergy (1.9%), drug hypersensitivity (1.5%), and hypersensitivity (1.5%).
- A total of 47 subjects (5.9%) reported treatment-emergent injection site reaction AEs. The most common of these AEs were injection site reaction (1.6%) and injection site erythema (1.4%).
- A total of 33 subjects (4.2%) reported treatment-emergent AEs associated with opportunistic infections. The most common opportunistic infections were oral candidiasis (2.8%) and candidiasis (1.1%).
- One subject (0.1%) reported a treatment-emergent serious opportunistic infection (oesophageal candidiasis).
- Two subjects (0.3%) reported treatment-emergent tuberculosis (TB) (reactivation of TB and miliary TB).
- Ten subjects (1.3%) reported treatment-emergent AEs associated with CHF. The most common AEs associated with CHF were cardiac failure (0.8%) and congestive cardiac failure (0.4%). There was one death due to congestive heart failure (CHF) (fatal CHF after TEP), which was considered unrelated to treatment with adalimumab.
- Six subjects (0.8%) reported treatment-emergent lupus or lupus-like reactions. Four subjects (0.5%) had lupus-like syndrome and two subjects (0.3%) reported cutaneous lupus erythematosus.
- A total of 334 subjects (42.1%) reported treatment-emergent hepatic-related AEs. The most common hepatic-related AEs were blood alkaline phosphatase increased (25.2%), aspartate aminotransferase increased (20.2%), and alanine aminotransferase increased (14.9%).
- One subject (0.1%) reported treatment-emergent serious blood dyscrasias (thrombocytopenia).
- Two subjects (0.3%) reported treatment-emergent demyelinating disease (moderate multiple sclerosis and demyelinating disorder).

Adalimumab was generally safe and well-tolerated as evaluated by assessments of serum chemistries, hematologic values, and coagulation parameters.

- Mean changes from Baseline suggest that treatment with adalimumab is associated with small mean increases from Baseline in hemoglobin and hematocrit, and decreases from Baseline in platelet counts. Mean changes from Baseline also suggest that treatment with adalimumab is associated with small mean decreases in WBC and neutrophil counts and small mean increases from Baseline in lymphocyte counts. The mean changes for these hematology parameters were all small, and were similar to those reported in adalimumab-treated subjects with RA or other primary conditions and are not clinically relevant.
- Review of the number of subjects with changes of potential clinical significance in hematology parameters demonstrate that clinically important changes are uncommon following treatment with adalimumab.
- Mean changes from Baseline suggest that treatment with adalimumab is associated with



increases in AST, total bilirubin, and serum triglycerides and with decreases in ALP. The mean changes from Baseline for these parameters were generally small and are not clinically relevant. Changes in values for triglycerides were similar to those reported for adalimumab-treated subjects with RA or other primary conditions.

- Only four subjects had elevations in ALT that met the potentially clinically significant criteria, each of whom also had AST elevations of potential clinical significance at the same timepoints as their ALT elevations. All four subjects had ALT and AST elevations as of the last evaluation, including a potentially clinically significant ALT elevation in one subject and potentially clinically significant AST elevations in two subjects. Each of the four subjects experienced hepatic-related AEs during the timeframe of their ALT elevations, three of whom included reports of SAEs.
- An equal proportion of subjects with a negative ANA titer at Baseline switched to positive compared with subjects with a positive ANA titer at Baseline who switched to negative.
- Mean changes from Baseline in systolic and diastolic blood pressure and pulse rate were all small and not clinically meaningful.

Conclusions:

Efficacy results from this open-label continuation study demonstrate that long-term administration of adalimumab results in: (1) maintained reduction of the signs and symptoms of RA; (2) maintained improvement in physical function; (3) maintained rates of clinical remission; and (4) maintained improvement in patient-reported quality of life.

Safety results from Study DE018 demonstrate that long-term administration of adalimumab is generally safe and well tolerated, regardless of whether 40 mg adalimumab is administered as an eow SC injection or more frequently at weekly dosing intervals; no new safety findings were observed during this long-term continuation study of adalimumab. Overall, the findings from this study suggest that there is no change to the risk benefit profile of long-term use of adalimumab.