2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Item of the Submission:**	
Name of Study Drug: Adalimumab	**Volume:**	
Name of Active Ingredient: Adalimumab	**Page:**	

Title of Study: A Prospective Multi-Center Randomized, Double Blind, Active Comparator-Controlled, Parallel-Group Study Comparing the Fully Human Monoclonal Anti-TNFα Antibody Adalimumab Given Every Second Week with Methotrexate Given Weekly and the Combination of Adalimumab and Methotrexate (MTX) Administered over 2 Years in Patients with Early Rheumatoid Arthritis (PREMIER)

Investigator:

Coordinating Investigator is:
Edward C. Keystone, MD
[redacted]

Study Sites:

One hundred thirty-two (132) sites in Australia, Austria, Belgium, Canada, Switzerland, Czech Republic, Germany, Denmark, Spain, Finland, France, United Kingdom, Ireland, Italy, Netherlands, Norway, Slovakia, Sweden, and US enrolled subjects.

Publications: 19

Studied Period (Years): 2-year blinded period, up to 8-year Open-label Extension (OLE) period. First Subject Enrolled Date: 12 December 2000 Last Subject Final Visit Date: 15 June 2012 (final 70-day follow-up completed)	**Phase of Development:** 3

Objective:

The objective of this study was to investigate the clinical efficacy and safety of 40 mg every other week (eow) subcutaneous (sc) injections of adalimumab in combination with MTX versus MTX monotherapy or adalimumab monotherapy in the treatment of early rheumatoid arthritis (RA).

Methodology:

This was a 10-year, multicenter, randomized, double-blind, active comparator-controlled, parallel-group, Phase 3 study of adalimumab in MTX-naïve subjects with early rheumatoid arthritis (RA) (defined as RA meeting American College of Rheumatology criteria and disease duration of less than 3 years). The first 2 years were randomized, double-blind (DB), and active comparator-controlled. Subjects were randomized 1:1:1 to one of three treatment groups: adalimumab 40 mg eow, adalimumab 40 mg eow together with weekly MTX (≤ 20 mg/week), or weekly MTX (≤ 20 mg/week) alone. Adalimumab administration was given sc while MTX was given orally. All subjects received oral concomitant folic acid 5 to 50 mg/week. The primary and major secondary analyses compared adalimumab + MTX combination therapy with MTX monotherapy. Adalimumab + MTX combination therapy and adalimumab monotherapy were compared for other secondary endpoints only.

The study included a Screening period, a 4-week washout period for subjects taking previous disease-modifying anti-rheumatic drugs (DMARDs), a blinded two-year treatment period, and an optional 8-year OLE for those who completed the blinded period, and during which all subjects received adalimumab. As follow-up, all subjects, irrespective of study completion or discontinuation, were to be examined at one month following their last dose of adalimumab.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 750 subjects

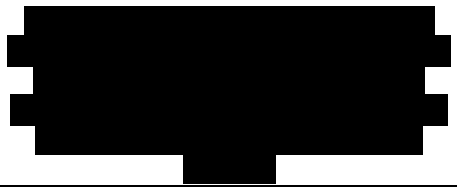
Analyzed: 799 subjects enrolled and randomized; 697 subjects receiving ≥ 1 dose of adalimumab (ITT)

Diagnosis and Main Criteria for Inclusion:

The major inclusion criteria for the study included subjects with the following: diagnosis with RA as defined by the 1987-revised American College of Rheumatology (ACR) classification criteria; a disease duration of < 3 years; ≥ 8 out of 66 swollen joints (SJC66) and ≥ 10 out of 68 tender joints (TJC68) assessed; and an erythrocyte sedimentation rate (ESR) ≥ 28 mm/lh or C-reactive protein (CRP) ≥ 1.5 mg/dL.

The major exclusion criteria for the study included subjects with the following: chronic arthritis diagnosed before age 16 years; prior treatment with MTX, cyclophosphamide, cyclosporin, azathioprine, or > 2 other disease-modifying anti-rheumatic drugs (DMARDs); serum creatinine > 1.5 mg/dL; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) outside 1.5 × upper normal laboratory range (ULN) or bilirubin ≥ 3 mg/dL; and hemoglobin < 9 g/dL for males and < 8.5 g/dL for females.

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

Study Drug	Study Drug for SC Injection: Formulation	Manufacturer	Bulk Lot Numbers
Adalimumab Pre-Filled Syringe	40 mg/0.8 mL 	Abbott	05-003742 05-002187 07-011080 07-011196 08-017131 09-025414 10-001959 10-000765
Adalimumab Vial Single-Use	40 mg/0.8 mL 	Abbott	180400AW 180500AW 88007HK 09146HK 04079HK 04080HK 12188HK 11172HK 25266HK 05-001031 05-000170
Adalimumab Vial Single-Use	40 mg/1.6 mL 	Abbott	080900A8 081110A8 080100A0 080200A0
Placebo for adalimumab		Abbott	180100PW 88006HK 080400P8 080500P8 980300P8

Subjects were randomized to 1 of 3 treatment groups: adalimumab 40 mg eow (adalimumab + placebo weekly), adalimumab 40 mg eow together with weekly MTX, or weekly MTX (MTX + placebo eow). After the completion of the 2-year DB period, subjects could enroll in the OLE during which they received OL adalimumab 40 mg eow.

Adalimumab administration was SC while MTX was given orally. Starting in 2006, OL adalimumab vials were subsequently replaced by prefilled syringes (40 mg adalimumab in 0.8 mL) for self injections, which were also to be given SC.

The dosing interval of the blinded study drug (adalimumab, placebo) was to be decreased from eow to weekly during the DB period in subjects who failed to respond, or who lost their response, on or after 16 weeks of treatment.

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

Oral study drug (MTX, placebo) was to be given weekly through Week 104. Oral MTX was started at 7.5 mg/week and was to have remained at this dose for 4 weeks. In the presence of any remaining swollen joints, the dose was to have been increased to 15 mg from Week 5 forward for an additional 4 weeks and to a total of 20 mg from Week 9 forward. A dose of 20 mg MTX was the highest dose permitted in this study.

Before decreasing the dosing interval of the adalimumab/placebo from eow to weekly, the dose of MTX/placebo must have been optimized (the highest tolerated dose was to be administered for ≥ 6 weeks). In the OLE, the Investigator could have titrated or de-escalated MTX based on his or her clinical judgment.

Duration of Treatment:

The total study duration was approximately 10 years (520 weeks) of adalimumab exposure and, in total, 529 weeks including the post-study follow-up period.

Criteria for Evaluation

Efficacy:

Primary Efficacy Variables

This study examined the efficacy and safety of adalimumab in combination with MTX versus MTX monotherapy in the treatment of early RA using two pre-specified endpoints. The two primary endpoints were:

- the proportion of subjects who achieved an ACR50 response at Week 52 between adalimumab + MTX combination therapy and MTX monotherapy; and
- the change from baseline in modified TSS between adalimumab + MTX combination therapy and MTX monotherapy at Week 52.

Major Secondary Efficacy Variables

Year 1 and 2

Major secondary endpoints comparing adalimumab + MTX combination therapy versus MTX monotherapy and adalimumab + MTX combination therapy versus adalimumab monotherapy, ranked in the following order, included:

1. Improvement of physical function as measured by the change from baseline in the Disability Index of the Health Activity Questionnaire (HAQ-DI) at Week 52.
2. Proportion of subjects who achieved an American College of Rheumatology (ACR)50 (a 50% improvement, based on ACR response criteria) response at Week 104.
3. Change from baseline in modified Total Sharp Score (mTSS) at Week 104.
4. Proportion of subjects who achieved clinical remission, defined as Disease Activity Score (DAS28) < 2.6 at Week 52.
5. Change from baseline in the physical component of the SF-36 v1® Health Status Survey (SF-36 v1®) at Week 52.

Criteria for Evaluation (Continued)

Year 1 and 2 (Continued):

6. Proportion of subjects achieving a major clinical response, defined as an ACR70 response for any six continuous months through Week 104.
7. Change from baseline in the mental component of the SF-36 v1® at Week 52.

Through Year 10

Endpoints through Year 10 were to include:

- ACR20/50/70 response by visit
- HAQ-DI score by visit
- DAS28 score by visit
- DAS28 remission (DAS < 2.6) and low disease activity (DAS28 < 3.2) by visit
- Change in mTSS at Year 10
- mTSS progression (change in mTSS > 0.5 and > 0)
- Composite score of ACR50 with no change in mTSS
- Major clinical response over Year 10
- Improvement in HAQ-DI ≥ 0.5 by visit

The following secondary efficacy variables were to be summarized (at Weeks 26, 52, 76, and 104, unless otherwise indicated) and compared if not previously specified. All comparisons were to be conducted using the testing of adalimumab + MTX combination therapy versus MTX monotherapy and adalimumab + MTX combination therapy versus adalimumab monotherapy: ACR20, ACR50, and ACR70; HAQ-DI (also at Week 12); HAQ-DI ≥ 0.3; Health Utilities Index Mark 2 and Mark 3 (HUI 2/3) and SF-36 v1® (not at Week 72); ACR-N (smallest percent change from baseline in the number of tender joint count [TJC68], swollen joint count [SJC66], the median percent improvement in Patient's Assessment of Pain, Physician's Global Assessment of Disease Activity (PGA), Patient's Global Assessment of Disease Activity, HAQ-DI, and CRP, and incorporation of all disease activity measures of the ACR response); DAS28; and change from baseline in modified TSS; change from baseline in erosion score; and change from baseline in joint space narrowing (JSN) score (all 3 not reported at Week 76); no worsening in modified TSS, erosion score; and JSN score (change from baseline in modified TSS, JSN score, and erosion score ≤ 0) for subjects who had no erosions at baseline; the percent who continued to have no erosions at Weeks 52 and 104; and for subjects who had non-involved joints at baseline, the percent who had no new involved joints at Weeks 52 and 104.

In addition, the following additional efficacy variables were to be summarized as change from baseline or percent change from baseline, as appropriate: TJC, SJC, HAQ-DI, duration of morning stiffness, PGA and Patient's Global Assessment of Disease Activity, Patient's Assessment of Pain, CRP, ACR20/50/70, ACR-N, DAS-28 (all by visit), and HUI 2/3 and SF-36 v1® (both at Weeks 12, 26, 42, and 52).

Pharmacokinetic:

Not applicable.

Criteria for Evaluation (Continued)

Safety:

All safety related information was collected and processed according to applicable regulatory guidelines. Subjects were monitored for clinical and laboratory evidence of adverse events (AEs) on a routine basis throughout the study period, defined as the interval between Visit 1 until the end of the 70-day follow-up period. AEs occurring between Visit 1 and first treatment with study medication were analyzed separately.

Statistical Methods:

All statistical tests in this study were performed at significance level $\alpha = 0.05$, two sided. The *P* values reported in the analysis of demographic parameters, secondary efficacy variables, other efficacy variables, and safety parameters are considered nominal.

Summary statistics are used to present data. Categorical data is described by the frequency and percentage; summaries of continuous data have been generated by displaying the mean, standard deviation, standard error, median, minimum, quartiles and maximum.

Efficacy:

In order to assess a possible bias caused by drop-outs, different approaches were used, e.g., all observed, imputation methods, last observation carried forward (LOCF) for completers only, as appropriate.

The first primary objective was to assess the efficacy of adalimumab + MTX combination therapy versus MTX monotherapy in reducing signs and symptoms in subjects with early RA. If this primary objective was met, the second primary analysis was to be performed to investigate whether adalimumab + MTX combination therapy was superior to MTX monotherapy in the inhibition of radiographic progression, as measured by change from baseline in modified TSS at Week 52.

χ^2-tests were used for analysis of the first primary efficacy endpoint. All subjects in the ITT Analysis Set were included. Subjects with missing values were considered non-responders. To assess the impact of subjects who dropped out of the study before Week 52, or lacked sufficient data for Week 52 ACR50 calculations, two sensitivity analyses were performed. In the first analysis, all data were summarized as observed without imputation for missing data (referred to as the "as observed" or "completer" analysis). In the second analysis, the last observation carried forward (LOCF) approach was used to impute ACR50 response. The most recent non-missing ACR50 response before Week 52 was used for subjects who missed Week 52 visit or lacked insufficient data at Week 52.

All secondary endpoints, as listed above, were analyzed to investigate the superiority of adalimumab + MTX combination therapy versus MTX monotherapy and adalimumab + MTX combination therapy versus adalimumab monotherapy. Analysis of the secondary endpoints was performed in a conditional manner, similar to the primary endpoint analyses, until a non-significant *P* value was reported. For continuous endpoints (e.g., DAS28), ANOVA or ANCOVA models were to be applied. For categorical endpoints (e.g., ACR20, ACR50 or ACR70), χ^2-tests for comparison of proportions (number and percentage) of subjects were to be used.

Analyses for long-term efficacy endpoints were based on subjects enrolled in the OLE. Information was to be reported for these subjects from the beginning of the study, which includes the DB period. Efficacy analyses were to be based on observed data. Radiographic data were to be presented for subjects who completed Year 10 of the study.

Statistical Methods (Continued):

Pharmacokinetic:

Not applicable.

Safety:

Analysis of safety was performed on all subjects in the ITT Analysis Set, which included all subjects who received ≥ 1 dose of study drug. In addition to the analysis of the complete ITT Analysis Set, a subgroup analysis for subjects without prior DMARDs was performed. Long-term safety data (treatment-emergent AEs [TEAEs]) are presented for subjects who had ≥ 1 dose of adalimumab during the study.

TEAEs were analyzed by frequency and percentage for all subjects who received ≥ 1 dose of study drug. TEAEs were defined as events with a start date on or after the date of the first study drug dose.

AEs that started more than 70 days after the last study drug dose were not included in the summaries. TEAEs of special interest, e.g., SAEs, or AEs leading to premature study discontinuation, were listed by treatment group and narratives were provided.

Vital signs and laboratory data were to be described by statistical characteristics and frequency of abnormal values. For laboratory data, the normal ranges of the analyzing laboratory were to be used. Values beyond the normal values were to be listed.

Statistical Methods (Continued):

Summary: Key demographic and baseline disease and efficacy characteristics are summarized below:

Demographic Characteristic		Any Adalimumab (ITT Analysis Set) (N = 697)
Age (years), Mean ± SD		52.1 ± 13.5
Sex, n (%)	Female	521 (74.7)
	Male	176 (25.3)
Race, n (%)	White	653 (93.7)
	Black	18 (2.6)
	Asian	93 (1.3)
	Other	17 (2.4)

		Any Adalimumab (ITT Analysis Set)	
Disease/Efficacy Characteristic	**n**	**Mean ± SD**	**Median (Range)**
Duration of RA (years)	695	0.8 ± 0.82	0.4 (0.0 – 3.8)
Duration of morning stiffness (mins)	615	121.7 ± 106.18	90.00 (2.0 – 360.0)
TJC68 (0 – 68 joints)	697	26.0 ± 16.43	25.0 (0 – 68)
SJC66 (0 – 66 joints)	697	18.0 ± 12.10	16.0 (0 – 63)
TJC28 (0 – 28 joints)	697	13.7 ± 8.07	14.0 (0 – 28)
SJC28 (0 – 28 joints)	697	11.9 ± 6.98	12.0 (0 – 28)
Subject's Assessment of Pain (0 – 100 mm VAS)	693	53.8 ± 28.80	57.0 (0 – 100)
Subject's Global Assessment of Disease Activity (0 – 100 mm VAS)	692	56.8 ± 29.81	62.0 (0 – 100)
PGA (0 – 100 mm VAS)	695	55.4 ± 27.41	62.0 (0 – 99)
HAQ-DI (0 – 3)	693	1.3 ± 0.74	1.4 (0.0 – 3.0)
DAS28(CRP) (> 5.1 = high disease activity)	692	5.6 ± 1.66	6.0 (1.5 – 8.6)
DAS28(ESR) (> 5.1 = high disease activity)	691	6.0 ± 1.77	6.5 (0.5 – 8.9)
Simplified Disease Activity Index (SDAI))	690	40.1 ± 20.08	42.1 (0.4 – 93.3)
Clinical Disease Activity Index (CDAI)	690	36.7 ± 18.32	38.8 (0.0 – 73.9)
CRP (mg/dL)	697	1.4 ± 3.85	1.8 (0.4 – 20.7)
ESR (mm/hr)	695	42.5 ± 26.88	37.0 (0.9 – 133.0)
RF (IU/mL)	685	358.0 ± 690.84	146.0 (20.0 – 8940.0)

Statistical Methods (Continued):

Efficacy Results:

This study evaluated the efficacy and safety of adalimumab + MTX, MTX alone, and adalimumab alone for the DB period and the efficacy and safety of adalimumab in the subsequent OLE period for up to 10 years in MTX-naïve subjects with early RA (defined as RA meeting the ACR classification criteria and disease duration < 3 years).

Reduction in Signs and Symptoms of RA, Improvement in Physical Function, Inhibition of Radiographic Progression, and Clinical Remission Within 2 Years

The analysis of both primary endpoints, the proportion of subjects who achieved an ACR50 response and the change from baseline in mTSS following 52 weeks of treatment, demonstrated that adalimumab + MTX combination therapy is clinically and statistically superior to MTX monotherapy in reducing the signs and symptoms of RA and inhibiting progression of radiographic progression in subjects with recently diagnosed moderate to severe RA.

Maintained Reduction of the Signs and Symptoms of RA:

Following 1 year of treatment, 61.6% of subjects who received adalimumab + MTX combination therapy achieved an ACR50 response compared to 45.9% of subjects who received MTX monotherapy ($P < 0.001$).

Inhibition of Radiographic Progression:

Following 1 year of treatment, subjects treated with adalimumab + MTX combination therapy had a mean mTSS increase of 1.3 compared to 5.7 in subjects treated with MTX monotherapy ($P < 0.001$).

Secondary Endpoints

All of the major secondary endpoints identified for the DB period (including change from baseline in the HAQ-DI (Year 1) and mTSS (Year 2) as well as the proportion of subjects who achieved an ACR50 response (Year 2), clinical remission defined as DAS28 < 2.6 (Year 1), and a major clinical response) demonstrated the statistical superiority of adalimumab + MTX combination therapy compared to MTX monotherapy, with the exception of the last ranked endpoint, the mental component of the SF-36 v1® at Week 52.

Furthermore, based on an analysis of other secondary efficacy variables assessed, adalimumab + MTX combination therapy was found to be clinically and statistically superior to MTX monotherapy and adalimumab monotherapy in improvement of signs and symptoms, inhibition of radiographic progression, improvement of physical function, achievement of clinical remission and major clinical response, reduction in disease activity, and improvement in the physical aspect of QoL.

Maintained Reduction in Signs and Symptoms of RA, Improvement in Physical Function, Minimal Radiographic Progression, and Clinical Remission up to 10 Years

Maintained Reduction of the Signs and Symptoms of RA

In the ITT Analysis Set (subjects who received at least 1 dose of adalimumab during the study for up to 10 years), ACR50 response rates (65.6% at Year 1 and 74.7% at Year 10) showed that reductions in the signs and symptoms of RA achieved following 1 year of adalimumab exposure were sustained with up to 10 years of exposure to adalimumab.

Statistical Methods (Continued):

Maintained Reduction of the Signs and Symptoms of RA (Continued):

Results from other efficacy measurements of RA assessed through Year 10 (ACR20/70/90/100 response rates, TJC68, SJC66, Subject's Assessment of Pain, Subject's Global Assessment of Disease Activity, PGA, CRP and ESR levels, RF levels, and duration/presence of morning stiffness) provided additional evidence that the reductions in the signs and symptoms of RA achieved following 1 year of adalimumab exposure were sustained with up to 10 years of adalimumab exposure as follows:

- ACR20/50/70/90/100 response rates were maintained through Year 10 (Year 1 response rates for ACR20/50/70/90/100 were 82.9%, 65.6%, 45.4%, 18.5%, and 5.6%, respectively and Year 10 response rates for ACR20/50/70/90/100 were 90.6%, 74.7%, 60.0%, 31.2%, and 8.8%, respectively).
- TJC68 and SJC66: Decreases (improvement) in TJC68 and SJC66 from baseline were maintained through Year 10. The change of –28.0 mm at Year 10 represents an 88.8% improvement in TJC68. The change of –18.2 mm at Year 10 represents an 86.7% improvement in SJC66.
- Subject's Assessment of Pain: Decreases (improvement) from baseline were maintained through Year 10 (change of –43.8 mm at Year 10 represents an improvement of 66.6% in the subjects' assessment of their pain).
- Subject's Global Assessment of Disease Activity: Decreases (improvement) from baseline were maintained through Year 10 (change of –46.3 mm at Year 10 represents an improvement of 70.0% in the subjects' assessment of their disease activity).
- PGA: Decreases (improvement) in PGA from baseline were maintained through Year 10 (change of –56.6 mm at Year 10 represents an 86.2% improvement in the PGA).
- CRP: Mean reduction (improvement) from baseline in CRP was generally maintained through Year 10 (–3.1 mg/dL change at Year 10; 75.7% improvement from baseline).
- ESR: Mean reduction (improvement) from baseline in ESR was generally maintained through Year 10 (–23.4 mg/dL change at Year 10; 26.7% improvement from baseline).
- RF: Mean reduction (improvement) from baseline in RF was maintained through Year 10 (–261.0 IU/mL change at Year 10; 55.5% improvement from baseline)
- Morning stiffness: At Year 1, 48.2% of subjects reported no morning stiffness; at Year 6, more than one-half of subjects (57.4%) reported no morning stiffness.

Subject dropouts occurred during the study, but did not negatively impact the ACR50 response, as subjects who left the study were representative of all responders. This result was consistent with the reason for discontinuation data, which showed that only a small percentage of subjects discontinued from the study for lack of efficacy.

Maintained Improvement in Physical Function

In the ITT Analysis Set, clinically significant reductions from baseline in mean HAQ DI score (–0.9 at both Year 1 and Year 10) showed that improvements in physical function achieved following Year 1 were sustained through Year 10. The mean change of –0.9 at Year 10 of adalimumab exposure represents a 62.8% improvement in physical function score.

Statistical Methods (Continued):

Maintained Improvement in Physical Function (Continued)

Results from HAQ-DI 0.22/0.50/0.75/1.0 response rates provided supportive evidence that the improvements in physical function achieved following Year 1 were sustained through Year 10. Additionally, during each year, a substantial proportion of subjects, ranging from 52.0% to 75.9%, were HAQ-DI responders (HAQ-DI 0.22) when they dropped out of the study. The proportion of dropouts who were HAQ-DI responders every year was either similar to or greater than the dropouts who were nonresponders.

Minimal Radiographic Progression

Minimal radiographic progression, as evidenced by relatively small increases seen in mTSS compared to baseline, was found from Year 2 up to Year 10 in subjects who received at least 1 dose of adalimumab during the study (ITT Analysis Set).

- At Year 2 of Study DE013, the mean changes from baseline in the total erosion score were ‑ 0.4 for subjects originally randomized to adalimumab + MTX, 3.4 for subjects originally randomized to MTX, and 2.7 for subjects originally randomized to adalimumab. By Year 10, mean changes from baseline in erosion scores for the 3 original randomized treatment groups were 1.2, 5.2, and 4.3, respectively, indicating that the smallest increases in erosion score by Year 10 occurred in subjects receiving adalimumab + MTX. Change in joint erosion from Year 2 to Year 10 during the OLE was minimal and comparable amongst the 3 randomized treatment groups.
- At Year 2, the mean changes from baseline in total JSN score were 0.7 for subjects originally randomized to adalimumab + MTX, 2.9 for subjects originally randomized to MTX alone, and 2.4 for subjects originally randomized to adalimumab. By Year 10, the mean changes from baseline in total JSN scores for the 3 original randomized treatment groups were 2.8, 5.7, and 4.9, respectively, indicating that the smallest increases in JSN score by Year 10 occurred in subjects receiving adalimumab + MTX. Change in JSN from Year 2 to Year 10 during the OLE was minimal and comparable amongst the 3 randomized treatment groups.
- At Year 2, the mean changes from baseline in mTSS score were 0.3 for subjects originally randomized to adalimumab + MTX, 6.3 for subjects originally randomized to MTX alone, and 5.1 for subjects originally randomized to adalimumab. By Year 10, the mean changes from baseline in mTSS scores for the 3 original randomized treatment groups were 3.9, 10.8, and 9.2, respectively, indicating that the smallest increases in mTSS score by Year 10 occurred in subjects receiving adalimumab + MTX. Change in mTSS from Year 2 to Year 10 during the OLE was minimal and comparable amongst the 3 randomized treatment groups.
- The proportions of Year 10 completers and early terminators who experienced no radiographic progression (defined as a change from baseline in mTSS ≤ 0.5) at Year 2 were 73.0%, 43.4%, and 43.5% for subjects originally randomized to adalimumab +MTX, MTX alone, and adalimumab alone, respectively. At Year 10, 36.7% of Year 10 completers or early terminators originally randomized to adalimumab + MTX still had experienced no radiographic progression compared with 31.3% of subjects randomized to MTX alone and 23.7% of subjects randomized to adalimumab alone. Using the end of the DB period (Year 2) visit as baseline, the proportions of Year 10 completers and early terminators who experienced no radiographic progression at Year 10 were increased (adalimumab + MTX, 38.2%; MTX alone, 48.2%; adalimumab alone, 46.7%) compared to the above proportions using the first visit as baseline.

Statistical Methods (Continued):

Maintained Rates of Clinical Response

Multiple assessments of clinical response (SDAI remission, Clinical Disease Activity Index (CDAI) remission, DAS28[CRP] and DAS28[ESR] remission, "Good" European League Against Rheumatism (EULAR)[CRP] and [ESR] responses, and major clinical response) showed that the rates of clinical response achieved after 1 year of adalimumab exposure were sustained through Year 10.

- The proportion of subjects who were in clinical remission based on SDAI (≤ 3.3) and CDAI (≤ 2.8) increased through Year 10 (49.4% at Year 10 for SDAI and 49.1% at Year 10 for CDAI). Furthermore, mean change from baseline at Year 1 in SDAI was –35.3 (–73.3%) and in CDAI was –32.7 (–73.7%); mean change from baseline at Year 10 of –39.7 in SDAI and –37.2 in CDAI represent an improvement of 85.4% from both the baseline SDAI and CDAI score.
- At Year 1, 42.7% of subjects were in clinical remission based on DAS28(CRP) < 2.6 criteria. The proportion of subjects in DAS28(CRP) remission continued to increase to a maximum of 68.4% at Year 10. Similar trends in clinical remission were seen when the DAS28(ESR) remission criteria was applied (36.6%, and 48.2% at Year 1 and Year 10, respectively).
- At Year 1, 59.6% of subjects had a "Good" EULAR(CRP) response (i.e., a DAS28 score of ≤ 3.2 at a current visit with a corresponding change from baseline of ≤ 1.2). The proportion of subjects with a "Good" EULAR(CRP) response continued to increase to a maximum of 84.8% at Year 10. Similar trends in "Good" EULAR(ESR) were seen when the EULAR(ESR) criteria was applied (51.1%, and 67.7% at Year 1 and Year 10, respectively).
- Over an 8 to 10 year period of exposure to adalimumab, 273 of 687 subjects (39.7%) demonstrated a major clinical response (i.e., maintenance of an ACR70 response for at least a 6-month continuous period at any time during the study following the first dose of adalimumab).

Impact of Changes in MTX and Oral CS Dosing on Adalimumab Efficacy

A total of 52.5% of subjects in the OL Subject Set (N = 497) used MTX during the OLE, with a mean weekly dose of 13.09 mg and a mean time on MTX of 66.1% of subject's entire OLE durations (introduction of MTX occurred at different time points for different subjects during the OLE). The impact of MTX use during the OLE on various efficacy variables including HAQ-DI score, remission criteria, DAS28(CRP), DAS28(ESR), and radiographic progression was assessed from Year 2 to Year 10. For all of these efficacy parameters (with the exception of radiographic progression which increased over time and HAQ-DI scores which stayed the same over time), subjects who did or did not use MTX during the OLE showed improvement over time. Subjects who did not use MTX during the OLE showed greater improvement than subjects receiving MTX during the OLE for all efficacy parameters, including for rates of radiographic progression and HAQ-DI scores.

Statistical Methods (Continued):

Impact of Changes in MTX and Oral CS Dosing on Adalimumab Efficacy (continued)

A total of 53.8% of subjects in the ITT Analysis Set (N = 697) received oral corticosteroids (CSs) during the study. Of these, 41.3% of subjects reduced their oral CS dose to zero by the final visit, while another 12.8% of subjects reduced their oral CS dose by their final visit. Subjects whose oral CS dose was reduced through Year 10 tended to have ACR response rates, HAQ-DI categorical response rates, clinical remission/response rates, and the proportions of subjects with no radiographic progression that were consistently higher compared with the subsets of subjects whose oral CS dose was unchanged or increased during the study. This is not unexpected since the oral CS dose was allowed to be reduced in those subjects who responded favorably to adalimumab and suggests that in those subjects whose oral CS dose was reduced, overall efficacy was not sacrificed (since the efficacy data were consistent with the results for the overall adalimumab-treated population). A substantial number of subjects were able to reduce their oral CS use over 8 to 10 years of treatment with adalimumab.

Safety Results:

A total of 23 of the 799 subjects enrolled in the study (all randomized subjects) died following up to 10 years in the study, including 1 subject (Subject [redacted]) who was randomized to MTX monotherapy (did not receive adalimumab during the study) and died during the DB period of cardiorespiratory stop. A total of 22 subjects who received at least 1 dose of adalimumab (ITT Analysis Set) died; of these, 17 subjects experienced TEAEs leading to death (≤ 70 days after last adalimumab dose), and an additional 5 subjects experienced non-TEAEs (> 70 days after last adalimumab dose) leading to death. TEAEs leading to death considered by the Investigator to be at least possibly related to study drug were reported in 8 subjects. For all randomized subjects (n = 799) with 23 deaths, the calculated standard mortality ratio (SMR) (95% CI) and an age-adjusted modified SMR (95% CI) were 0.72 (0.49, 1.02) and 0.45 (0.31, 0.64), respectively. Comparable SMR and modified SMR results were found for the ITT Analysis Set compared to those calculated for all randomized subjects. In both analysis sets, calculations resulted in an SMR below 1.0, which indicates that the observed number of deaths is below what would be expected in an age-, sex-, and country-matched population.

Through 10 years of adalimumab exposure, approximately one-half (45.9%) of subjects who received at least 1 dose of adalimumab during the study experienced a serious AE (SAE) and 22.5% of subjects experienced a TEAE that led to discontinuation of study drug. The most frequently reported SAEs were RA (worsening of), osteoarthritis, and pneumonia. The most frequently reported TEAEs leading to discontinuation of study drug were: RA, ALT increased, pneumonia, arthritis bacterial, pleural effusion, and AST increased.

A total of 97.3% of subjects who received at least 1 dose of adalimumab during the study experienced at least one TEAE up to Year 10 of Study DE013; the majority (72.2%) of subjects experienced a TEAE that was considered by the Investigator to be at least possibly study drug related. Through up to 10 years of adalimumab exposure, 43.0% of subjects experienced a severe AE.

Safety Results (Continued):

A total of 79.5% and 11.2% of subjects who received at least 1 dose of adalimumab during the study experienced infection-related TEAEs and serious infection-related TEAEs, respectively. The most frequently reported infection-related TEAEs were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, and sinusitis. The most frequently reported serious infection related TEAEs were pneumonia, lobar pneumonia, cellulitis, bronchitis, sepsis, arthritis bacterial, and bronchopneumonia.

A total of 8.3% of subjects had serious treatment-emergent infections that were considered by the Investigator to be at least possibly study drug related. Pneumonia (10 subjects) and lobar pneumonia, sepsis, and arthritis bacterial (4 subjects each) were the most frequently reported treatment-emergent serious infections considered by the Investigator to be at least possibly study drug-related.

The most frequent TEAEs were reported in the AE of special interest category of infection (83.0 E/100 PYs). Following infections, events were most frequently reported in the categories of liver failure and other liver TEAEs, injection site reaction related TEAEs, and serious infection-related TEAEs (E/100 PYs of 4.0, 5.0, and 2.6, respectively).

One subject who received at least 1 dose of adalimumab during the study had an opportunistic infection-related TEAE excluding oral candidiasis and TB. The event was mycobacterium avium complex infection; it was considered by the Investigator to be possibly study drug related and severe, and led to discontinuation of study drug.

Active tuberculosis (TB) was reported in 3 subjects who received at least 1 dose of adalimumab during the study. All 3 subjects with active TB were serious, severe, and considered to be at least possibly related to study drug by the Investigator. TB test conversion was reported in 3 subjects who received at least 1 dose of adalimumab during the study. All 3 subjects with TB test conversion had events of tuberculin test positive; the events were non-serious and mild or moderate in severity; 2 of the 3 events were considered to be possibly related to study drug by the Investigator and were unresolved by the final evaluation. All 3 subjects with TB test conversion were treated for TB prophylaxis.

The proportions of subjects who received at least 1 dose of adalimumab during the study with any non-melanoma skin cancer (NMSC), any lymphoma, and other malignancies (excluding lymphoma, hepatosplenic T-cell lymphoma (HSTCL), leukaemia, NMSC, and melanoma) were 4.0%, 0.9%, and 4.2%, respectively. The most frequently reported NMSCs were basal cell carcinoma (22 subjects) and squamous cell carcinoma (7 subjects). Of the other malignancy TEAEs, the most frequently reported events were breast cancer (5 subjects) and renal cell carcinoma (3 subjects). Six subjects had malignancies that resulted in death; these malignancies included non-small cell lung cancer stage IV, colon cancer stage IV, ovarian cancer, lung neoplasm malignant, hepatic neoplasm, and metastases to the liver. Across all clinical cancer sites, the Standardized Incidence Ratio (SIR) for malignancies was lower than expected given the population evaluated (0.89 [95% CI: 0.62 – 1.26]). However, the SIR for all lymphomas and squamous cell NMSCs were markedly elevated (3.75 [95% CI: 1.37 – 8.15] and 2.69 [95% CI: 1.23 – 5.11], respectively). The SIR for overall NMSCs however was more similar to expected rates (1.74 [95% CI: 1.21 – 2.42]).

Two subjects who received at least 1 dose of adalimumab during the study had demyelinating disorder TEAEs of optic neuritis; both cases were considered to be possibly study drug-related, led to discontinuation of study drug, and remained ongoing at the final evaluation.

Safety Results (Continued):

No subject in the ITT Analysis Set was reported to have had TEAEs of HSTCL, leukaemia, Stevens-Johnson syndrome (SJS), adalimumab administration-related medication error, reactivation of Hepatitis B, sarcoidosis, progressive multifocal leukoencephalopathy (PML) or reversible posterior leukoencephalopathy (RPL) syndrome, or amyotrophic lateral sclerosis (ALS).

In general, the majority of the most frequently reported treatment-related TEAEs, including TEAEs of special interest, SAEs, and TEAEs that resulted in discontinuation of study drug, are either consistent with the safety profile described in the currently approved prescribing information for adalimumab, are associated with the disease of interest, or are common in a middle aged population that has been evaluated for up to a 10 year period. Therefore, no new safety findings were observed in this study with long-term adalimumab treatment.

Small mean changes from baseline in hematology and chemistry parameters were similar to those described previously for subjects treated with adalimumab and do not appear to represent clinically important effects. Modest increases in triglycerides are believed to be due to a correction of the dyslipoproteinemia associated with the inflammatory state of RA.

Mean changes from baseline in vital sign values (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, and temperature) collected through Week 328 were small and not clinically meaningful.

Conclusions:

Efficacy results from the 10 year Study DE013 demonstrate that administration of adalimumab for up to 10 years in subjects with recently diagnosed moderate to severe RA resulted in:

- maintained reduction of the signs and symptoms of RA;
- minimized radiographic progression;
- maintained improvement in physical function; and
- maintained rates of clinical remission and major clinical response

Safety results from the 10 year Study DE013 demonstrated that administration of adalimumab for up to 10 years was safe and generally well tolerated. No new safety findings and a lower number of deaths than would be expected in an age-, sex-, and country-matched population were observed in this study with up to 10 years of adalimumab exposure.

Given the substantial benefit of improvement in signs and symptoms, minimization of radiographic progression, improvement of physical function, induction and maintenance of major clinical response and clinical remission, overall high rate of reduced disease activity achieved, and acceptable safety profile, the benefit risk profile in the treatment of subjects recently diagnosed with moderate to severe RA, with adalimumab with or without concomitant MTX therapy, is demonstrated to be strongly positive.