DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

BLA:	125057
Name of drug:	Adalimumab
Indication:	treatment for juvenile rheumatoid arthritis (JRA)
Applicant:	Abbott
Dates:	Letter 04/27/2007; PDUFA 02/27/2008
Review priority:	S (supplement)
Biometrics division:	Division of Biometrics II
Statistical reviewer:	Joan Buenconsejo, Ph.D.
Concurring reviewers:	Dionne Price, Ph.D.
Medical division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Clinical team:	Larissa Lapteva, M.D.
	Jeffrey Siegel, M.D.
Project manager:	Sharon Turner-Rinehardt
Keywords:	NDA review, clinical studies

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The applicant, Abbott Laboratories, has proposed the use of adalimumab as a treatment for juvenile RA in patients [redacted]. The evidence taken from study DE038 reviewed indicated that subjects with JRA who were administered adalimumab experienced less disease flares than did subjects who were administered placebo, regardless of their methotrexate (MTX) status.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Adalimumab, a human anti-TNF monoclonal antibody, is currently approved for treatment of rheumatoid arthritis (RA) in adults (approved December 31, 2002). Indication extensions to include treatment of psoriatic arthritis (approved October 03, 2005), and ankylosing spondylitis (approved August 28, 2006) were also approved subsequently. Adalimumab is additionally approved for use in Crohn's disease (CD) (approved February 27, 2007). The Applicant, Abbott Laboratories, seeks to obtain marketing approval for adalimumab as a treatment for juvenile RA in pediatric patients, also called juvenile idiopathic arthritis (JIA) in the European Union (EU). This supplement fulfills the postmarketing commitment (PMC) number 1 from sBLA 125057/16 that states "continue study DE038, a multi-center, randomized, double-blind placebo-controlled study of the safety and efficacy of human anti-TNF monoclonal antibody adalimumab in children with polyarticular juvenile rheumatoid arthritis."

The adalimumab clinical program comprised one randomized withdrawal, double-blind, stratified, parallel-group study in children (4 to 7 years old) with polyarticular JRA. There are four phases in the study: a 16-week open lead-in phase (OL-LI), a 32-week double-blind phase (DB), an open-label body surface area (OLE BSA) extension phase, and an open-label extension fixed dose (OLE FD) phase. Subjects were stratified into two groups, methotrexate (MTX)-treated or non-MTX-treated, depending on their MTX use prior to study enrollment. Subjects in the MTX stratum were treated concomitantly with MTX during the study. Subjects who were in the non-MTX stratum were either naïve to MTX or had been withdrawn from MTX at least two weeks prior to study drug administration and were not treated concomitantly with MTX during the study.

This study was designed to examine and compare disease flare in non-MTX adalimumab-treated polyarticular JRA subjects to non-MTX placebo-treated polyarticular JRA subjects who had previously responded to adalimumab treatment. Disease Flare is defined as subject who met the criteria for disease flare if they had both the following:

- >30% worsening in at least three of the six JRA core set criteria and also a minimum of two active joints.
- >30% improvement in not more than one of the six JRA core set criteria.

Subjects who dropped out prior to the end of the study were considered to have experienced a disease flare regardless of treatment group or reason. The primary endpoint was analyzed using the Pearson's chi-square test. . Two analyses using different approaches to handle missing data were also performed on the primary endpoint.

1.3 STATISTICAL ISSUES AND FINDINGS

There are no major statistical issues in this sBLA submission that could not be handled by recoding and re-analyzing the data. There were a few discrepancies found in the results provided in the study report and after re-analyses of the data. However, these discrepancies did not alter or affect the overall efficacy conclusion of adalimumab as a treatment for juvenile RA in pediatric patients.

2 INTRODUCTION

2.1 OVERVIEW

Adalimumab, a human anti-TNF monoclonal antibody is currently approved for treatment of rheumatoid arthritis (RA) in adults (approved December 31, 2002). Indication extensions to include treatment of psoriatic arthritis (approved October 03, 2005), and ankylosing spondylitis (approved August 28, 2006) were also approved subsequently. Adalimumab is additionally approved for use in Crohn's disease (CD) (approved February 27, 2007). The Applicant, Abbott Laboratories, seeks to obtain marketing approval for adalimumab as a treatment for juvenile RA in pediatric patients, also called juvenile idiopathic arthritis (JIA) in the European Union (EU).

The development plan for the treatment of JRA was introduced to the Division of Anesthesia, Analgesia, and Rheumatoid Products under BB-IND [redacted]. A pre-supplemental biologics license application meeting with the Division was held on February 1, 2007 to discuss the planned content and format for the sBLA and the preliminary efficacy, safety, and pharmacokinetic data from Study DE038. The key milestones in the clinical development program are highlighted in Dr. Lapteva's review. Statistical issues were discussed in the Pre-BLA meeting on February 1, 2007 and key issues are summarized below:

a. Last observation carried forward (LOCF) analysis of PEDACR responders during the DB phase.
b. Summary of weight-adjusted based on the OLE FD baseline for subjects in the OLE FD phase.
c. Summary of PEDACR responders by weight-adjusted dose (mg/kg) based on the OLE FD baseline, reported as percentile of subjects.
d. Overview of subjects with treatment-emergent AEs by weight-adjusted dose (mg/kg) based on OLE FD baseline, reported as percentile of subjects
e. Calculated cumulative dose of adalimumab (mg) for each phase.

This submission included one randomized withdrawal, double-blind, stratified, parallel-group study in children (4 to 7 years old) with polyarticular JRA. Subjects were stratified into two groups, methotrexate (MTX)-treated or non-MTX-treated, depending on their MTX use prior to study enrollment.

2.2 DATA SOURCES

This statistical review is based on data submitted in study DE038.

The electronic submission of this BLA can be found at:
\\cbsap58\M\EDR Submissions\2007 BLA\DCC60004694\125057

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The clinical program comprised one randomized withdrawal, double-blind, placebo-controlled, parallel-group study (conducted from September 19, 2002 to August 1, 2006) in children (4 to 17 years old) with polyarticular JRA. Subjects were stratified into two groups, MTX-treated or non-MTX-treated, depending on their MTX use prior to study enrollment. Subjects in the MTX stratum were treated concomitantly with MTX during the study. Subjects who were in the non-MTX stratum were either naïve to MTX or had been withdrawn from MTX at least two weeks prior to study drug administration and were not treated concomitantly with MTX during the study.

The primary efficacy objective of this study was to determine and compare disease flare (which will be defined in the following section) in non-MTX adalimumab-treated polyarticular JRA subjects to non-MTX placebo-treated polyarticular JRA subjects who had previously responded to adalimumab treatment.

3.1.1 STUDY DESIGN AND ANALYSIS PLAN

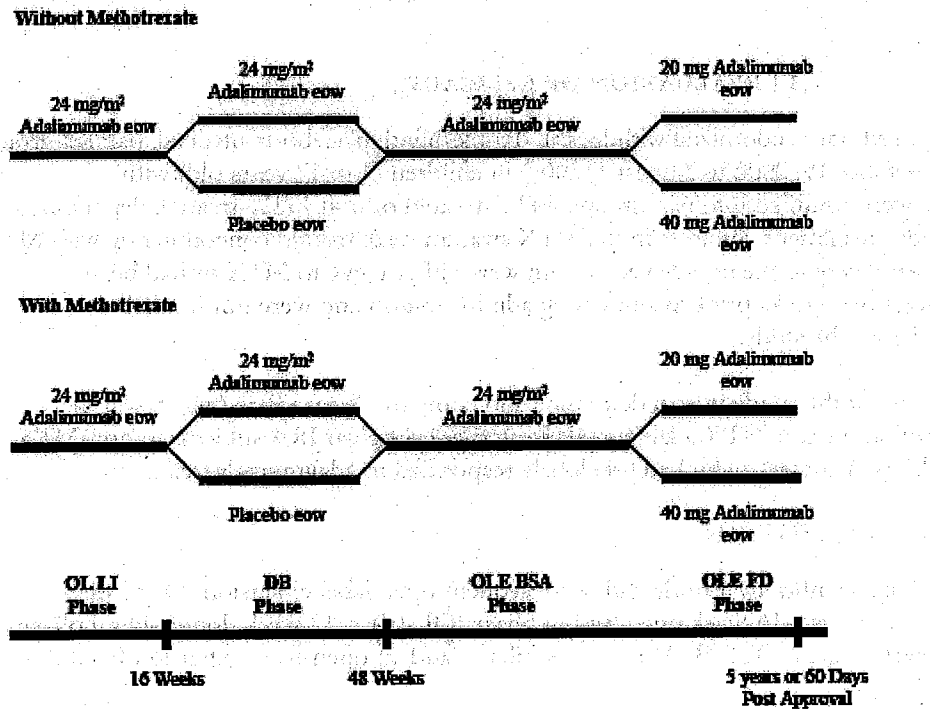
Study DE038 was a randomized withdrawal study with a subsequent open label extension (OLE) phase. There were four phases in the study: a 16-week open lead-in phase (OL-LI), a 32-week double-blind phase (DB), an open-label body surface area (OLE BSA) extension phase, and an open-label extension fixed dose (OLE FD) phase.

According to the Applicant,

> A total of 171 subjects enrolled into the 16-week OL-LI phase, in which each subject received 24 mg/m^2 of adalimumab (based on subject's BSA) subcutaneously (SC) every other week (eow) up to a maximum total body dose of 40 mg. The withdrawal from the study drug occurred at Week 16 of the OLE-LI phase at which time subjects that achieved a PedACR30 response were randomized within their stratum in a 1:1 ratio to placebo or adalimumab treatment arms of the 32-week DB phase of the study. BSA dosing continued to the DB phase. Subjects who experienced disease flare during the DB phase were eligible to immediately enroll into the open-label extension BSA (OLE-BSA) phase without completing the entire 32 weeks. These subjects, along with the subjects who completed the entire 32 weeks in the DB phase were eligible to participate in the OLE BSA phase and received adalimumab using the BSA dosing regimen. Subjects in the OLE BSA phase at the time of approval of the OLE FD protocol amendment were eligible to receive a fixed dose of either 20 mg or 40 mg eow adalimumab based on their body weight. Duration of the OLE BSA phase varied for each subject. Some subjects received adalimumab for up to 136 weeks. For each subject the actual exposure depended on when they flared during the DB phase and when they entered the OLE FD phase. Entry into the OLE FD phase depended on timing of approval of the OLE FD protocol amendment by the respective investigator review board (IRB).
>
> The OLE FD phase was implemented to gather safety and efficacy data on a fixed dosing regimen based on body weight in support of marketing approval. In the OLE FD phase, subjects with a body weight below 30 kg receive a fixed dose of 20 mg adalimumab eow and subjects with a body weight equal or above receive a fixed dose of 40 mg adalimumab eow. Subjects may continue the OLE FD phase for a maximum of five years or up to sixty days post marketing approval of the JRA indication in their respective country.

A schematic of the study design for Study DE038 is displayed in Figure 1.

Figure 1: Study Design of DE038



OL LI – open-label lead in; DB = double-blind; OLE BSA = open-label extension body surface area; OLE FD = open-label extension fixed dose

Source: 2.5 Clinical Overview, page 162

Efficacy Endpoints

The primary efficacy endpoint was the proportion of adalimumab-treated subjects in the non-MTX stratum who experienced disease flare during the DB phase. The JRA core set of variables listed below were used to determine disease flare.

- Physician's Global Assessment of subject's disease severity by visual analog scale (VAS)
- Parent's Global Assessment of subject's overall well-being by VAS
- Number of active joints (joints with swelling not due to deformity or joints with limitation of motion (LOM) and with pain, tenderness or both)
- Number of joints with LOM
- Disability index of childhood health assessment questionnaire (DICHAQ)
- C-reactive protein (CRP)

Subjects met the criteria for disease flare if they had both of the following:

- ≥30% worsening in at least three of the six JRA core set criteria and also a minimum of two active joints
- ≥30% improvement in not more than one of the six JRA core set criteria

Note that the DB baseline was used as the reference point for the disease flare calculation. Also, change in CRP value from baseline was evaluated for clinical improvement or worsening only if at least one of the CRP values, baseline value, or the visit value was outside the normal reference range. If both CRP values were within the normal reference range, a formal CRP evaluation of improvement or worsening was not done.

Protocol-defined secondary efficacy measures include:

- The proportion of subjects with disease flare by the end of the DB phase (week 48) for subjects treated with MTX
- Time to onset (from DB baseline) of flare by the end of the DB phase (week 48) for subjects treated without MTX.
- Time to onset (from DB baseline) of flare by the end of the DB phase (week 48) for subjects treated with MTX
- The proportion of subjects with a PedACR30 response at Week 16
- The proportion of subjects with a PedACR30/50/70/90 response at the end of the DB phase (Week 48)
- The proportion of subjects with a PedACR30/50/70/90 response in the OLE BSA phase
- The proportion of subjects with a PedACR30/50/70/90 response in the OLE FD phase

The PedACR30 response in OL LI phase and DB phase was defined as subjects who met the criteria if they had both of the following:

- ≥30% improvement in at least three of the six JRA core set criteria and also a minimum of two active joints
- ≥30% worsening in not more than one of the six JRA core set criteria

where the percent change is calculated at 100x(visit value – baseline value)/(baseline value).

Analysis Population

The efficacy and safety analyses were performed in an intent-to-treat (ITT) population, defined as all subjects who received at least one dose of study drug in the OL LI phase.

The four populations that were used to analyze different phases are:

- OL-LI: any ITT subject that received at least dose of adalimumab in the OL LI phase of the trial
- DB: any ITT subject that received at least one dose of DB medication
- OLE BSA: any ITT subject that received at least dose of adalimumab in the OLE BSA phase
- OLE FD: any ITT subject that received at least dose of adalimumab at an fixed dose of 20 mg or 20 mg

Sample Size

Although the Applicant planned to enroll 168 subjects to enter the OL-LI phase of the study, resulting in a total of 116 subjects (58 per stratum, 29 per treatment group) during the DB phase, a total of 171 subjects entered the OLE-LI phase and were included in the efficacy and safety analysis. From the OLE-LI phase, 133 subjects were randomized into the DB phase and were included in the analysis for both efficacy and safety through Week 48. Meanwhile, 128 subjects enrolled into the OLE BSA phase and 106 subjects enrolled into the OLE FD phase.

The sample size of 168 subjects was calculated to detect a difference in the proportion of subjects between placebo and the active adalimumab dose group who would experience disease flare assuming a placebo rate of 70% versus a rate of 30% in the active group. Assuming a binomial distribution, an alpha of 0.05, 80% power, two-sided test, and an initial monotherapy responder rate of 70%, a minimum of 29 subjects were needed per treatment arm within the appropriate strata during the DB phase. In order to achieve a sample of 29 subjects per arm within each stratum, 42 subjects need to be enrolled for each treatment group within each stratum.

Statistical Analysis

The primary efficacy variable was analyzed by comparing the proportion of subjects in the non-MTX stratum who had experienced a disease flare. The analysis was done using either Pearson's chi-square test or Fisher's exact test, as appropriate. A secondary analysis of the disease flare was done using logistic regression to estimate the odds ratio of disease flare while adjusting for use of steroid and NSAIDs at OL LI baseline.

Analyses of the secondary efficacy variables were done using analysis of covariance (ANCOVA) using OL LI baseline as the covariate and Chi-square test for discrete variables. For the analysis of "time to disease flare", a log-rank test was performed and the Kaplan-Meier curve for time to disease flare was generated.

The study protocol and the Statistical Analysis Plan for Study DE038 were amended during the course of the study. The following were the changes to the planned statistical analyses:

A. For the randomized withdrawal phase
   - Disease flare was determined for blinded subjects at DB baseline
   - The disposition of subjects who were PEDACR30 responders but did not enroll into the DB phase was analyzed
   - The AE overview data was analyzed for the combined OL LI and DB phases by event per 100/patient years
   - Most frequent (>5%) infectious AEs were analyzed by events per 100 PYs
   - Summary data for Tanner staging was done instead of comparison data
   - The inclusion of PEDACR90 response criteria

B. For the OLE phase:
   1. The inclusion of PEDACR90 response criteria

C. The following are additional post hoc analyses conducted by the Applicant:
   a. Last observation carried forward analysis of PEDACR responders during the DB phase.
   b. Summary of the weight-adjusted doses based on the OLE FD baseline for subjects in the OLE FD phase.
   c. Summary of PEDACR responders by weight-adjusted dose (mg/kg) based on the OLE FD baseline, reported as percentile of subjects
   d. Overview of subjects with treatment-emergent AEs by weight-adjusted dose (mg/kg) based on the OLE FD baseline, reported as percentile of subjects
   e. Calculated cumulative dose of adalimumab (mg) for each phase.

No adjustment for multiplicity was proposed for the secondary endpoints.

Handling of Missing Data

To account for the dropouts for the 'disease flare' endpoint during the DB phase, the following imputation techniques were used:

Imputation 1 (Primary): Subjects will be considered to have experienced a 'disease flare' if they drop out before the end of the study irrespective of the treatment group and the reason for discontinuation

Imputation 2 (sensitivity): Same as imputation 1 except for subjects in the placebo group who discontinue the study because of the primary reason other than flare (for example, adverse events) will be considered non-flared.

Imputation 3 (sensitivity): The imputation will be done using the last observation carried forward (LOCF) approach for the disease flare.

To account for the dropouts for the pediatric ACR response analysis, subjects will be considered as a 'non-responder' if they drop out before the end of the phase.

3.1.2 PATIENT CHARACTERISTICS AND DISPOSITIONS

Patient Disposition

The disposition of the 171 subjects who enrolled in Study DE038 is summarized in Figure 2.

A total of 160 subjects completed the OL LI phase. Subjects who were PedACR30 responders were eligible to continue to the DB phase. An analysis of PedACR30 responders at Week 16 is presented in Table 1. At Week 16, the Applicant calculated that there were 80 (94%) subjects in the MTX stratum and 64 (74 %) subjects in the non-MTX stratum who were PedACR30 responders for a total 144 PEDACR30 responders. Recalculation of PEDACR30 at Week 16 using the raw data yielded 141 total PEDACR30 responders (78 in the MTX group and 63 in the Non-MTX).

Table 1: PEDACR30 responders at Week 16 (ITT population)

	MTX N=85	Non-MTX N=86	Overall N=171
Applicant's	80 (94%)	64 (74%)	144 (84%)
Reviewer's	78 (92%)	63 (73%)	141 (82%)

Applicant Source: Clinical Study Report, page 266

Of the 160 subjects who completed the OL LI phase, 27 subjects did not enroll into the DB phase, which includes those three subjects who did not meet the PEDACR30 responder criteria based on my recalculation. These 27 subjects includes 16 subjects who did not meet the PedACR30 response criteria and 11 subjects who did not enroll into the DB phase for the following primary reasons: lack of efficacy (2; 7.4%), withdrawal of consent (2; 7%), protocol violations (2; 7%), occurrence of an AE(s) (1; 4%), and other (4; 15%). Those three misclassified subjects did not enroll in the DB and the reason was coded as 'Others'.

A total of 128 subjects completed the DB phase and entered the OLE BSA phase. There were 106 subjects who completed the OLE BSA phase and entered the OLE FD phase.

Adverse events and lack of efficacy were the most notable reasons for discontinuation. In the OL LI phase, 3 (2%) subjects discontinued due to AEs (2 (2%) subjects in the non-MTX stratum and 1 (1%) subject in the MTX stratum). Six of the 171 (4%) subjects all in the non-MTX stratum discontinued the study due to lack of efficacy.

Fewer subjects in the non-MTX stratum entered the DB phase compared to the MTX stratum (N=58 for non-MTX; N=75 for MTX). No subjects discontinued due to AEs or lack of efficacy during the DB phase.

In the OLE BSA phase, two subjects discontinued due to AEs (1 (3%) subject in the MTX stratum who was adalimumab-treated during the DB phase and 1 (4%) subject in the non-MTX stratum who was placebo-treated during the DB phase). Four (3%) subjects in the OLE BSA phase discontinued due the lack of efficacy (3 [8%] subjects in the MTX stratum previously placebo-treated and 1 [4%] subject in the non-MTX stratum previously placebo-treated).

In the OLE FD phase, 1 (4%) subject in MTX stratum whose dose remained the same (20 mg) as it was in the OLE BSA discontinued due to AEs. No subjects discontinued from the OLE FD phase due to lack of efficacy.

The number (%) of subjects in each analysis set by strata is presented in Table 2.

Table 2: Analysis Sets

A. Open-Label Lead-in Phase, N(%)

Analysis Set	All Adalimumab		Total
	MTX	Non-MTX	Adalimumab
	N=86	N=85	N=171
ITT	86 (100)	85 (100)	171 (100)
Safety	86 (100)	85 (100)	171 (100)

Source: Clinical Study Report, page 210

B. Double-Blind Phase

Analysis Set	MTX		Non-MTX		Total
	Adalimumab	Placebo	Adalimumab	Placebo	
	N=38	N=37	N=30	N=28	N=133
ITT	38 (100)	37 (100)	30 (100)	28 (100)	133 (100)
Safety	38 (100)	37 (100)	30 (100)	28 (100)	133 (100)

Source: Clinical Study Report, page 211

C. Open-Label Extension Body Surface Area Phase

Analysis Set	MTX		Non-MTX		Total
	Adalimumab	Adalimumab (Placebo during DB)	Adalimumab	Adalimumab (Placebo during DB)	
	N=35	N=36	N=29	N=28	N=128
ITT	35 (100)	36 (100)	29 (100)	28 (100)	128 (100)
Safety	35 (100)	36 (100)	29 (100)	28 (100)	128 (100)

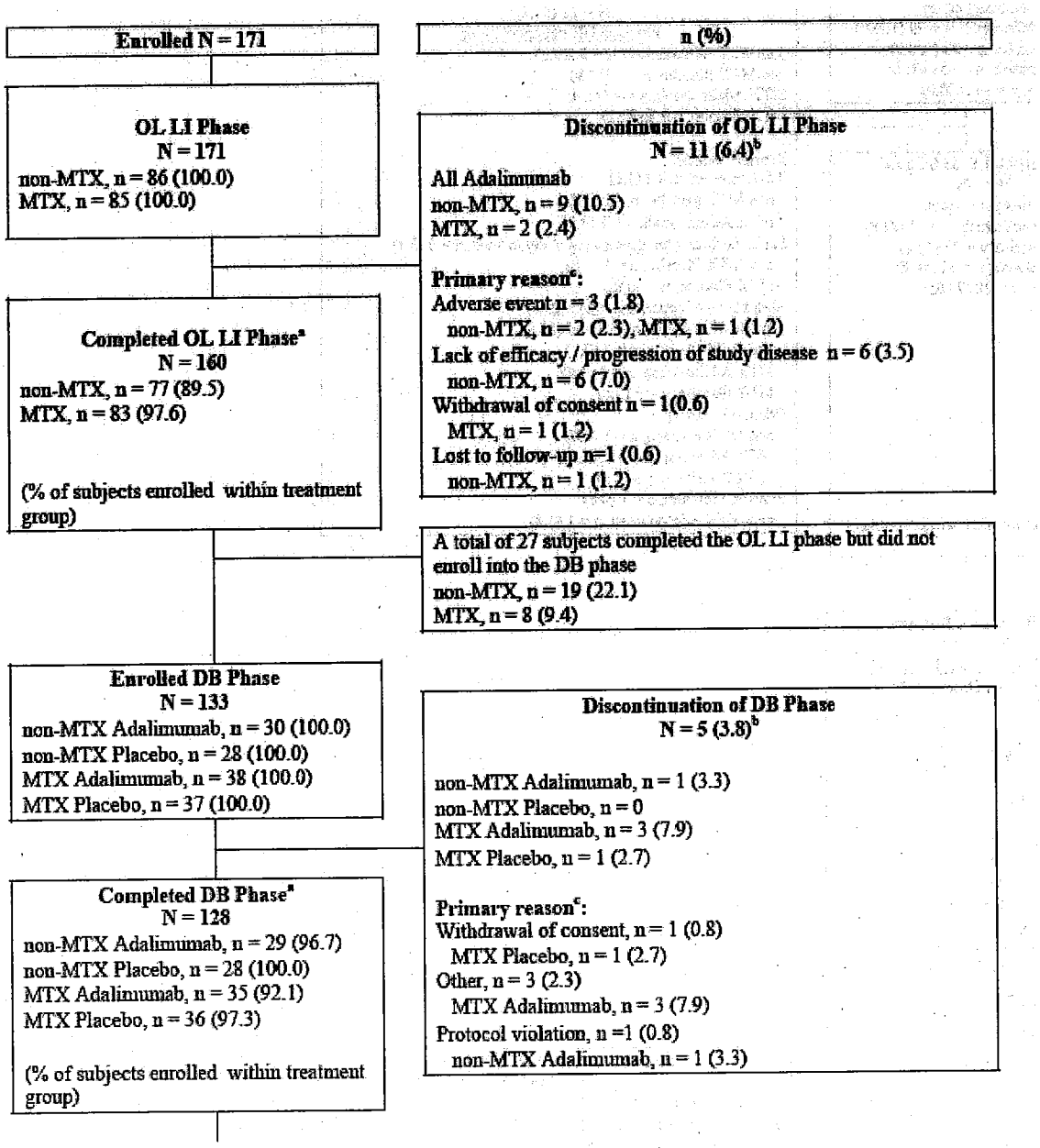
Source: Clinical Study Report, page 211

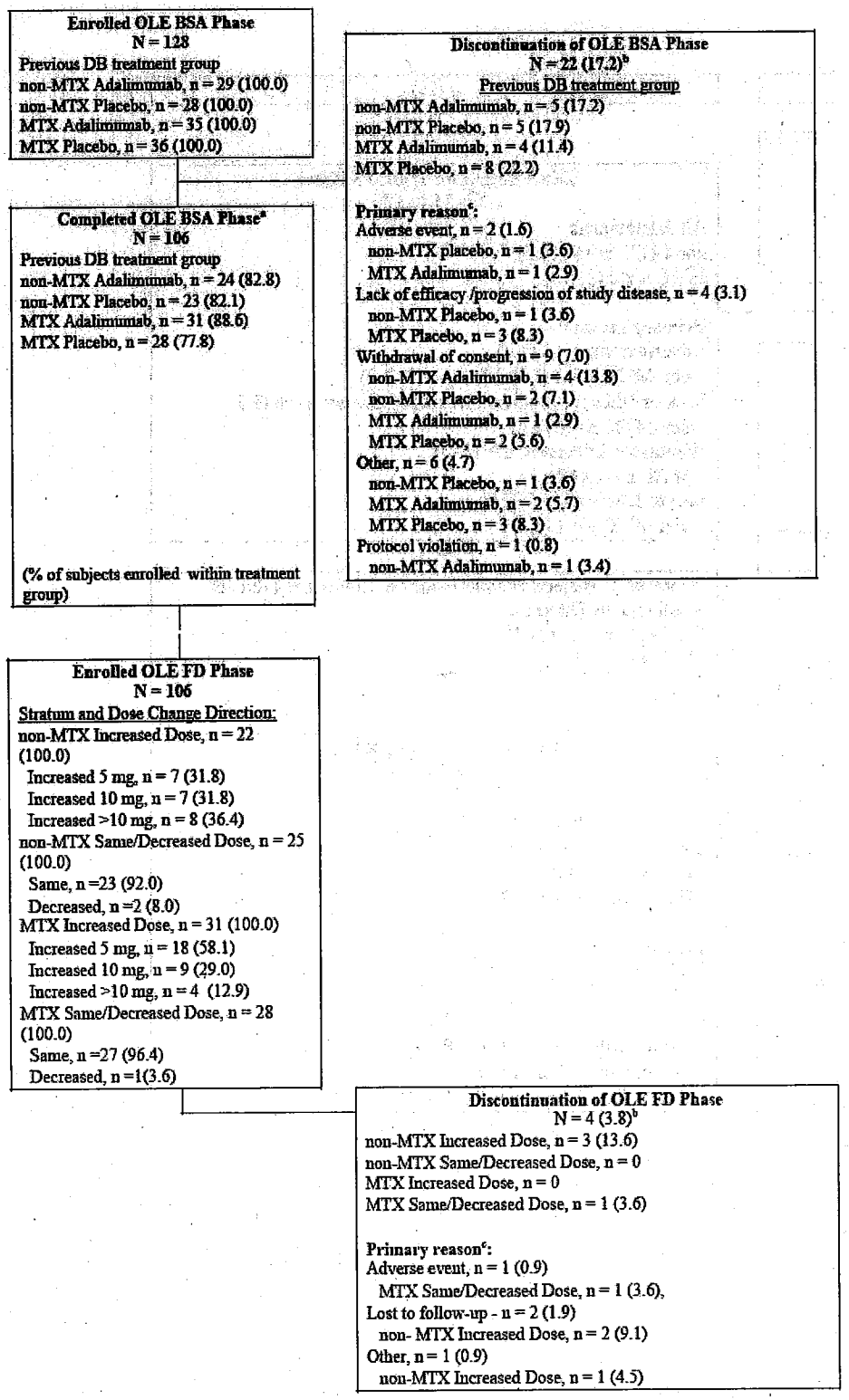
D. Open-Label Extension Fixed Dose

	MTX		Non-MTX		Overall		Total
	Same/ Decreased	Increased Dose	Same/ Decreased	Increased Dose	Same/ Decreased	Increased Dose	
	N=28	N=31	N=25	N=22	N=53	N=53	N=106
ITT	28 (100)	31 (100)	25 (100)	22 (100)	53 (100)	53 (100)	106 (100)
Safety	28 (100)	31 (100)	25 (100)	22 (100)	53 (100)	53 (100)	106 (100)

Source: Clinical Study Report, page 212

Figure 2: Subject Disposition





a. % of subjects enrolled within treatment group.

b. % of total subjects enrolled in that particular phase.

c. % of subjects within strata-treatment group.

Source: Clinical Study Report, page 205 - 207

Patient characteristics

The following is a short summary of patients' demographic and disease characteristics from the individual phases taken from the Study Report. Note that the Applicant calculated the patient's baseline characteristics based on their baseline open-label lead-in scores (e.g. age, Tanner Score, weight, height, tender joint count, swollen joint count, pain on passive motion joint, active joint count, limitation of passive motion joint count, etc.) in order to know how the baseline characteristics were distributed before anybody received any treatment for the four populations (i.e. Lead-in, Double-Blind, Open-Label extension and the Fixed Dose phase).

> In the OL-LI phase, the majority of patients were white (92%) and female (79%), with an overall mean age of 11 years (range 4 to 17 years). Mean weight was 42.3 kg and mean BMI was 19.4 kg/m^2. Subjects were distributed equally between the MTX and non-MTX stratum. Mean duration of JRA at baseline of this phase was 3.8 years. Mean tender joint count (TJC) was 11.4 based upon assessment of 75 joints, and mean swollen joint count (SJC) was 14.8 based upon an assessment of 66 joints. For all visual analog scale (VAS), a score of zero indicates no activity and a score of 100 indicates maximal activity. Mean parent's assessment of pain was 49.5 mm on VAS. Mean parent's global assessment of disease activity was 48.3 mm on VAS, and mean physician's global assessment of disease activity was 58.9 mm on VAS. Mean C-reactive protein (CRP) was 2.6 mg/dL. Mean childhood health assessment questionnaire disability index (DICHAQ) was 1.1. In general, subjects in the MTX stratum had lower disease activity at baseline.
>
> There were 133 subjects who were randomized into the DB phase. Fewer subjects in the non-MTX stratum entered the DB phase compared to subjects in the MTX stratum. The majority of the subjects who participated were white, female and had an approximate mean age of 11.4 years. Within each stratum, the demographic characteristics for placebo and adalimumab-treated subjects were very similar. Like in the OL-LI phase, subjects in the MTX stratum had lower disease activity compared to the non-MTX stratum. Meanwhile, within each stratum, the disease activity for placebo and adalimumab-treated subjects were very similar.
>
> There were 128 subjects who enrolled in the OLE BSA phase. All subjects in this phase received adalimumab. A similar proportion of subjects entered the OLE BSA phase from the placebo and the adalimumab treatment groups of the DB phase. Within each stratum, the demographic and disease characteristics for subjects randomized to placebo and adalimumab in the DB phase were very similar.
>
> There were 106 subjects n the OLE-FD phase. Subjects received changed in dose from the OLE BSA phase based on their weight. Subjects who weighed < 30 kg received 20 mg adalimumab eow and subjects who weighed > 30 kg received 40 mg adalimumab eow. Within the respective strata, and overall, there is a difference in the means for age and weight, as well as the mean of the Tanner score between subjects whose doses stayed the same or decreased compared to those whose doses were increased. However, the mean values for these parameters between strata were comparable. This was expected because it was more likely that older and heavier kids were already on the 40 mg dose during the OLE BSA phase based on the subject's BSA. Furthermore, younger children at a lower Tanner stage were expected to increase their dose compared to the older /heavier subjects who were at a higher stage of maturation and did not change their dose. Meanwhile, within the stratum, there was no difference between the same/decreased dose group and the increased dose group in disease activity except for the presence of rheumatoid factor (RF).

Exposure to Study Medication

In terms of exposure to study medication, all subjects who participated in the study received at least one injection of adalimumab 24 mg/m^2 BSA. According to the applicant,

> Mean cumulative dose of adalimumab received by all subjects in the OL LI phase was 232.4 mg and 369.1 mg for adalimumab-treated subjects in the DB phase. In the OLE BSA phase mean cumulative dose of adalimumab for subjects who were treated with adalimumab during the DB phase was 1417.8 mg and 1369.3 mg for subjects who received placebo during the DB phase. During the first 16 weeks of the OLE FD phase, mean cumulative adalimumab dose for subjects whose dose stayed the same or decreased was 309.4 mg and was 332.8 mg for subjects whose adalimumab dose increased compared to their OLE BSA dose. Subjects were exposed to adalimumab for a mean of 95 days in the OL LI phase, 157 days in the DB phase, and 627 days in the OLE BSA phase.

Subjects in the DB phase who flared were switched to OL adalimumab. The duration of exposure for the placebo-treated subjects in the DB phase was a mean of 128 days. In the OLE BSA phase, subjects who were previously treated with placebo in the DB phase had mean duration of adalimumab exposure of 614 days. Subjects in the OLE FD phase whose adalimumab dose stayed the same or was decreased had duration of a mean of 113 days and a mean of 108 days for subjects whose dose increased. Subjects whose dose increased 5 mg, 10, and > 10 mg had a mean duration of exposure in days of 110, 113, and 97, respectively.

3.1.3 SUMMARY OF RESULTS

3.1.3.1 Evaluation of disease flare

The primary efficacy endpoint was the proportion of adalimumab-treated subjects in the non-MTX stratum who experienced disease flare in the DB phase. Subjects who dropped out prior to the end of the study were considered to have experienced a disease flare regardless of treatment group or reason (Imputation # 1). A statistically significant lower proportion of adalimumab-treated subjects (71%) demonstrated disease flare compared to placebo-treated subjects (43%) in the non-MTX stratum (Table 3).

Sensitivity analyses using different approaches to handle missing data were also conducted on the primary endpoint. First, subjects with missing values were treated as having a disease flare except for the placebo-treated subjects who reported a primary reason for discontinuation other than disease flare (Imputation # 2). Since no subjects in the non-MTX stratum withdrew for reasons other than disease flare, results for imputation # 2 are the same as the primary analysis. Finally, an LOCF analysis was performed (Imputation # 3). The result from LOCF shows consistent result as the primary analysis; a significantly lower proportion of adalimumab-treated subjects (30%) demonstrated disease flare compared to placebo-treated subjects (70%) in the non-MTX stratum.

Table 3: Disease Flare during the Double-Blind Phase (ITT population, non-MTX stratum)

Analysis	Non-MTX		
	Adalimumab N=30	Placebo N=28	p-value[a]
Primary (Imputation # 1)	13 (43%)	20 (71%)	0.031
Imputation # 2	13 (43%)	20 (71%)	0.031
Imputation # 3	9 (30%)	19 (70%)	0.004

[a] The p-value is based on the Chi-square test.

Source: Clinical Study Report page 261 - 262

Logistic regression using a similar imputation done for primary analysis was also conducted by the Applicant to explore whether the prior use of steroids or NSAIDs could influence the incidence of disease flares in adalimumab-treated subjects. The results for predicting disease flares in adalimumab-treated subjects with prior use of steroids or NSAIDs are summarized in Table 4. The sensitivity and logistic regression analyses support the primary efficacy analysis and consistently demonstrated the superiority of adalimumab over placebo in decreasing disease flare.

In both the non-MTX and MTX strata, adalimumab was superior to placebo in reducing the odds of a disease flare (odds ratio = 0.2; 95% CI: 0.1 – 0.6 in the non-MTX stratum and odds ratio = 0.3; 95% CI: 0.1 – 0.7 in

the MTX stratum) after controlling for NSAID or corticosteroid use. Prior use of NSAIDs or corticosteroids did not seem to have an impact on disease flare.

Table 4: Logistic regression for the disease flare with regard for the use of steroids or NSAIDS (ITT population)

Variable	Odds Ratio[a]	95% CI[b]	p-value[c]
Non-Methotrexate			
Intercept			0.66
Adalimumab	0.2	0.1 – 0.6	0.00
NSAIDs	1.7	0.4 – 6.8	0.43
Corticosteroids	3.2	0.4 – 24.6	0.26
Methotrexate			
Intercept			0.71
Adalimumab	0.3	0.1 – 0.7	0.01
NSAIDs	1.4	0.4 – 4.9	0.57
Corticosteroids	1.4	0.5 – 4.1	0.51
Overall			
Intercept			0.98
Adalimumab	0.2	0.1- 0.5	0.00
NSAIDs	1.5	06. – 3.8	0.36
Corticosteroids	1.4	0.6 – 3.4	0.48

NSAIDs = non-steriodal anti-inflammatory drugs

a. Adalimumab estimate is reported in reference to placebo. NSAIDs and corticosteroids are binary variables (1= Yes, 0 = No).

b. Variable is statistically significant if the 95% confidence interval excludes 1.0.

c. The p-value is based on Chi-square test of maximum likelihood estimate for each variable.

Cross Reference: DE038 Section 14, Tables 14.2__23.1 through 14.2__23.3.

Source: Clinical Study Report page 263

3.1.3.2 Evaluation of protocol-defined secondary efficacy measures

The following subsections described the results on the protocol-defined secondary endpoints. Note that the Applicant did not apply any multiplicity adjustments to the statistical tests performed on these secondary endpoints.

A. Analysis and Comparison of Disease Flare

1. The proportion of subjects with disease flare by the end of the DB phase (week 48) for subjects treated with MTX

Like the non-MTX stratum, a lower proportion of adalimumab-treated subjects (37%) demonstrated disease flare compared to placebo-treated subjects (65%) in the MTX stratum (Table 5).

Sensitivity analyses were also conducted to this endpoint. Subjects with missing values were treated as having a disease flare except for the placebo-treated subjects who reported a primary reason for discontinuation other than disease flare (Imputation # 2). Since only one subject in the MTX stratum withdrew for reasons other than disease flare in the placebo arm, then results for imputation # 2 are almost the same as the primary

analysis. Finally, an LOCF analysis was performed (Imputation # 3). The result from LOCF shows consistent result as the primary analysis; a significantly lower proportion of adalimumab-treated subjects (21%) demonstrated disease flare compared to placebo-treated subjects (54%) in the MTX stratum.

Table 5: Disease Flare during the Double-Blind Phase (ITT population, MTX stratum)

Analysis	MTX		
	Adalimumab N=38	Placebo N=37	p-value[a]
Primary (Imputation # 1)	14 (37%)	24 (65%)	0.015
Imputation # 2	14 (37%)	23 (62%)	0.028
Imputation # 3	8 (21%)	20 (54%)	0.003

[a] The (unadjusted) p-value is based on the Chi-square test.

Source: Clinical Study Report page 261 - 262

2. Time to onset (from DB baseline) of flare by the end of the DB phase (week 48) for subjects treated without MTX.

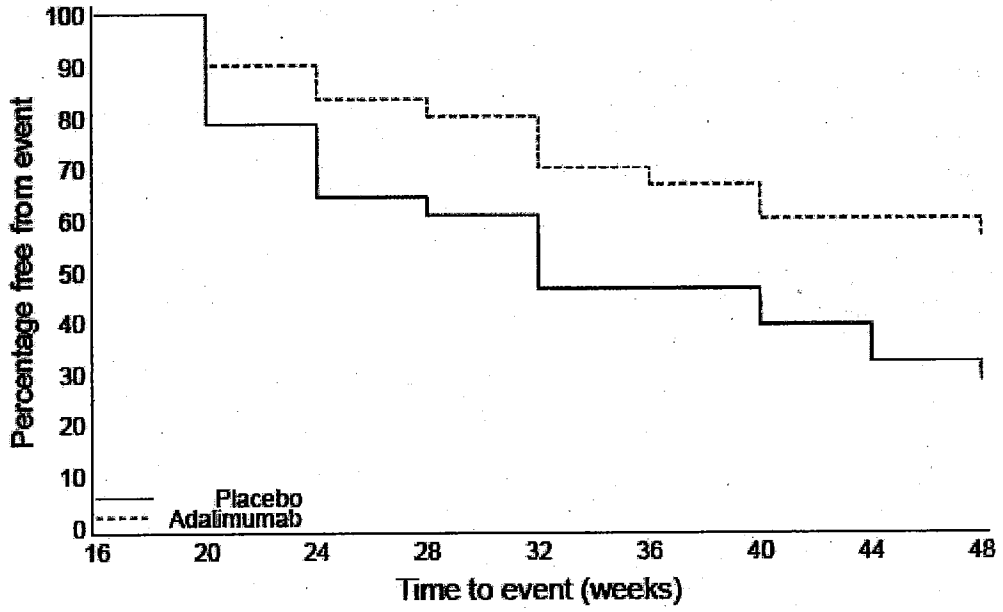
Subjects in the non-MTX stratum were compared by treatment group for the time of onset to disease flare during the DB phase. The Applicant presented the time to disease flare in the non-MTX and the MTX strata between treatment groups. I find that the Applicant's reported flare times of one subject in the non-MTX stratum and four subjects in the MTX stratum were different from my recalculation of flare onset (Table 6)

Table 6: Discrepancies in the Time to Disease Flare

Subject	Treatment Group	Applicant Reported Flare time	Reviewer Reported Flare time
Non-MTX			
DE038327013105	Adalimumab	40	44
MTX			
DE038USA000503704	Placebo	36	32
DE038USA0005636302	Placebo	28	24
DE038USA0005699107	Adalimumab	28	24
DE038USA0005911613	Adalimumab	24	20

Nonetheless, there is evidence that adalimumab was superior in delaying the onset of disease flare compared to placebo in the non-MTX stratum (Figure 3 and Table 7). The median time to disease flare from the first dose of DB treatment was more than 32 weeks for subjects in the adalimumab treatment group and about 14 weeks for subjects who received placebo.

Figure 3: Kaplan-Meier Curve of Time to Disease Flare, Comparison between Treatment Groups (ITT Population, Double-Blind Phase non-MTX Stratum)



Source: Clinical Study Report, Figure 2 page 267

The following table presents the time to disease flare for subjects in the non-MTX stratum. There was a slight difference between the Applicant's calculation and the Reviewer's calculation of the 'percent without disease flares' due to one subject in the Adalimumab that flared at least once but was not reported by the Applicant. However, this difference does not appear to affect the overall findings in the non-MTX stratum.

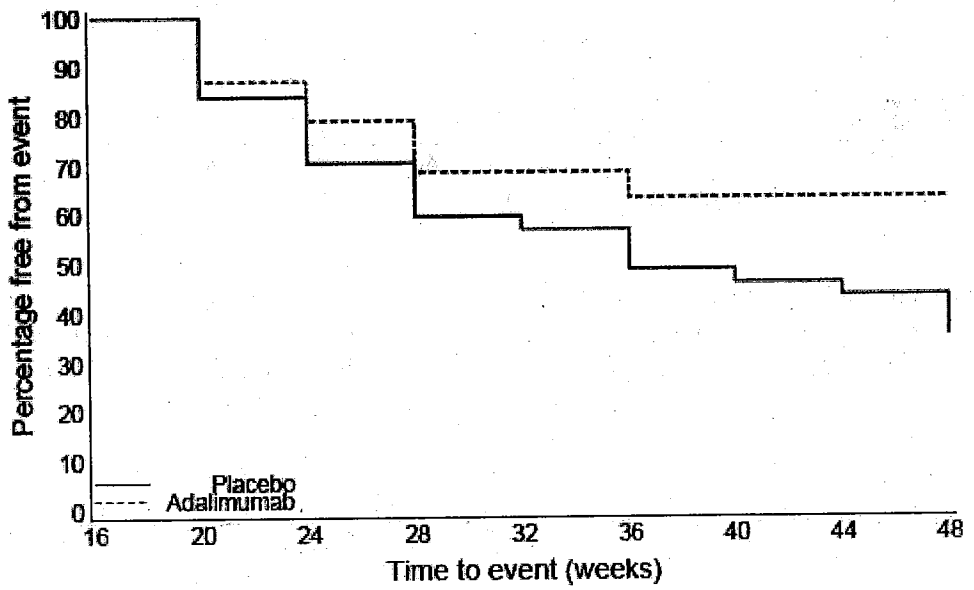
Table 7: Time to Disease Flare in the Double-Blind Phase (ITT Population, non-MTX stratum)

		% without disease flares			
		Applicant's		Reviewer's	
Study Visit Week	Weeks since randomization	Adalimumab N=30	Placebo N=28	Adalimumab N=30	Placebo N=28
20	4	90	79	90	79
24	8	83	64	83	64
28	12	80	61	80	61
32	16	70	46	70	46
36	20	67	46	67	46
40	24	60	39	63	39
44	28	60	32	60	32
48	32	57	29	57	29
p-value (log-rank)		0.029		0.028	

3. Time to onset (from DB baseline) of flare by the end of the DB phase (week 48) for subjects treated with MTX

Subjects were compared by treatment for the time of onset to disease flare during the DB phase. The time to the onset of disease flare for subjects in the MTX stratum is presented in Figure 4 and Table 8. Adalimumab was superior to placebo in delaying the time of onset of disease flare for subjects in the MTX stratum. The median time to disease flare from the first dose of DB treatment was more than 32 weeks for subjects receiving adalimumab and about 20 weeks for subjects receiving placebo. Despite the discrepancies shown in Table 7, the Kaplan-Meier curve and the median time to disease flare in the both treatment group remained the same.

Figure 4: Kaplan-Meier Curve of Time to Disease Flare, Comparison between Treatment Groups (ITT Population, Double-Blind Phase MTX Stratum)



Source: Clinical Study Report, Figure 3 page 270

The following table presents the time to disease flare for subjects in the MTX stratum. There was a slight difference between the Applicant's calculation and the Reviewer's calculation of the 'percent without disease flares', this difference does not appear to affect the overall findings in the MTX stratum.

Table 8: Time to Disease Flare in the Double-Blind Phase (ITT Population, MTX stratum)

		% without disease flares			
		Applicant's		Reviewer's	
Study Visit Week	Weeks since randomization	Adalimumab N=38	Placebo N=37	Adalimumab N=38	Placebo N=37
20	4	87	84	84	84
24	8	79	70	76	68
28	12	68	60	68	59
32	16	68	57	68	54
36	20	63	49	63	49
40	24	63	46	63	46
44	28	63	43	63	43
48	32	63	35	63	35
p-value (log-rank)		0.031		0.034	

B. Continued Clinical Benefit

1. The proportion of subjects with a PedACR30/50/70/90 response in the Double-Blind Phase

The PedACR30/50/70/90 responses were used to monitor the improvement or worsening of JRA symptoms in subjects throughout the study. From the time that a subject drops out or flares, they are counted as non-responders. The denominator for each strata and treatment group is based on the ITT population (i.e. number of subjects who enrolled in the DB phase). A minor discrepancy between the study report and the results obtained after re-analysis of the data is observed in the MTX stratum at Week 48 for PEDACR30/50/70/90 (two in the placebo group and two in the Adalimumab group, Table 9). Summaries of the analyses of responders for the PEDACR30/50/70/90 during the DB phase are presented by methotrexate strata and treatment groups in Figure 5 - Figure 8. Summaries of the analyses of responders for the PEDACR30/50/70/90 in tabular form are presented in Appendix 1.

Table 9: Discrepancies in PEDACR30/50/70/90 in the Double-Blind Phase (ITT Population, MTX stratum)

Subject	DE038USA0005071103 (Adalimumab)		DE038USA0005911614 (Placebo)	
	Sponsor	Reviewer	Sponsor	Reviewer
PEDACR30	Yes	No	No	Yes
PEDACR50	Yes	No	No	No
PEDACR70	Yes	No	No	No

Subject	DE038USA0005574208 (Adalimumab)		DE038USA0004947109 (Placebo)	
	Sponsor	Reviewer	Sponsor	Reviewer
PEDACR90	No	Yes	Yes	No

Results demonstrated that at most time points during the DB phase, a greater proportion of subjects who received adalimumab in the MTX and the non-MTX stratum were PedACR30/50/70/90 responders compared to subjects who received placebo (Figure 5 - Figure 8). There is strong evidence that a greater proportion of placebo-treated subjects lose the PEDACR30 and PEDACR50 response compared to adalimumab-treated subjects over time, regardless of MTX status. Meanwhile, for more stringent criteria of response (i.e. PEDACR70 and PEDACR90), the MTX-adalimumab group appeared to maintain their response from Week 16 up to Week 48. While there was a slight benefit in the non-MTX adalimumab group over time, the proportion of responders are not that different from the placebo groups.

Figure 5: PEDACR30 Response by Stratification and Treatment Group for the DB Phase

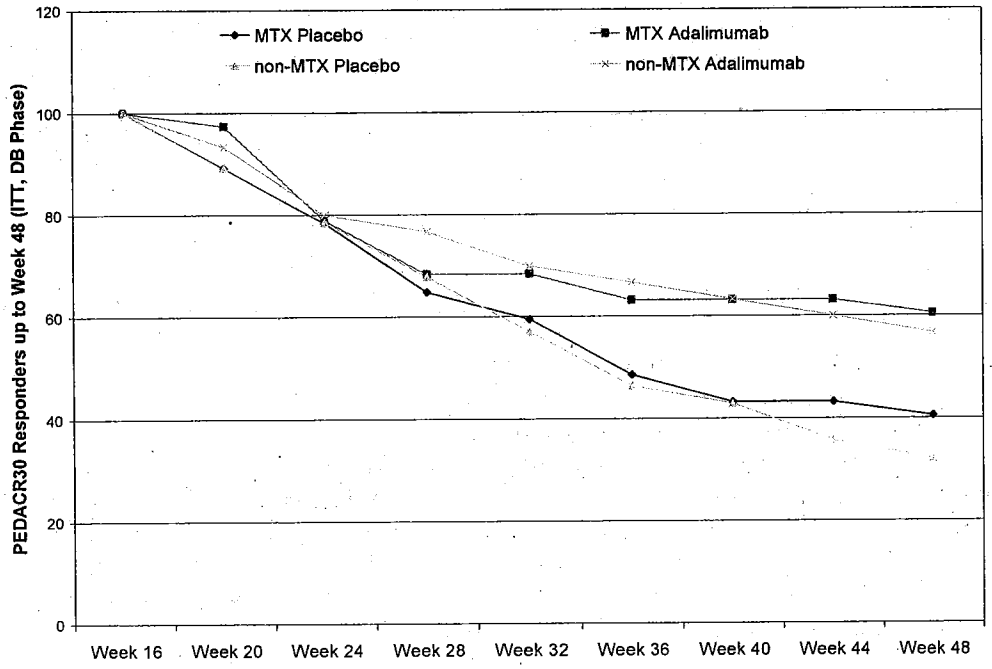


Figure 6: PEDACR50 Response by Stratification and Treatment Group for the DB Phase

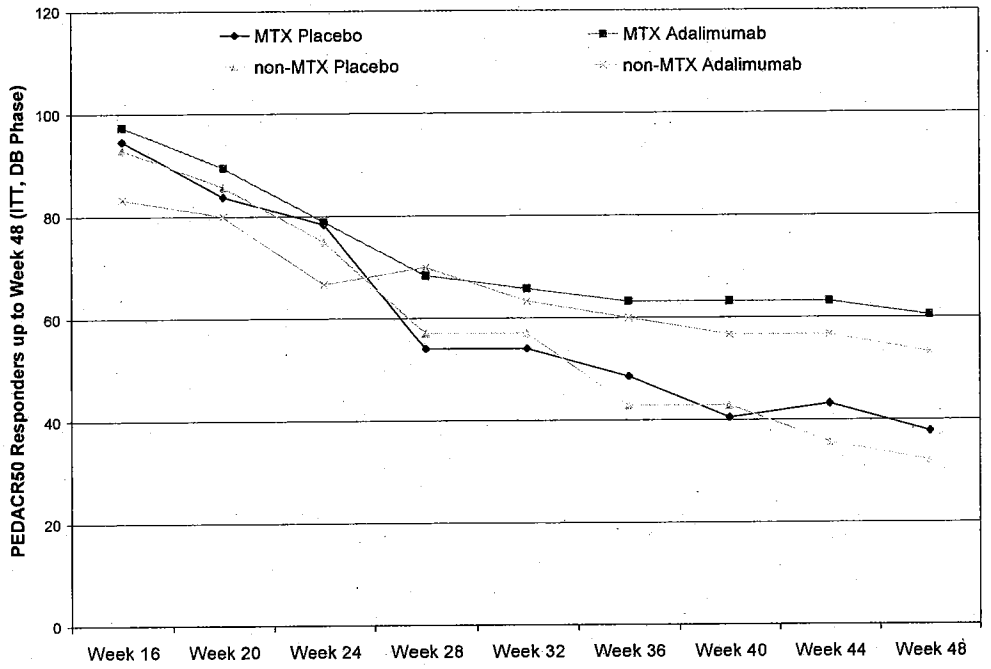


Figure 7: PEDACR70 Response by Stratification and Treatment Group for the DB Phase

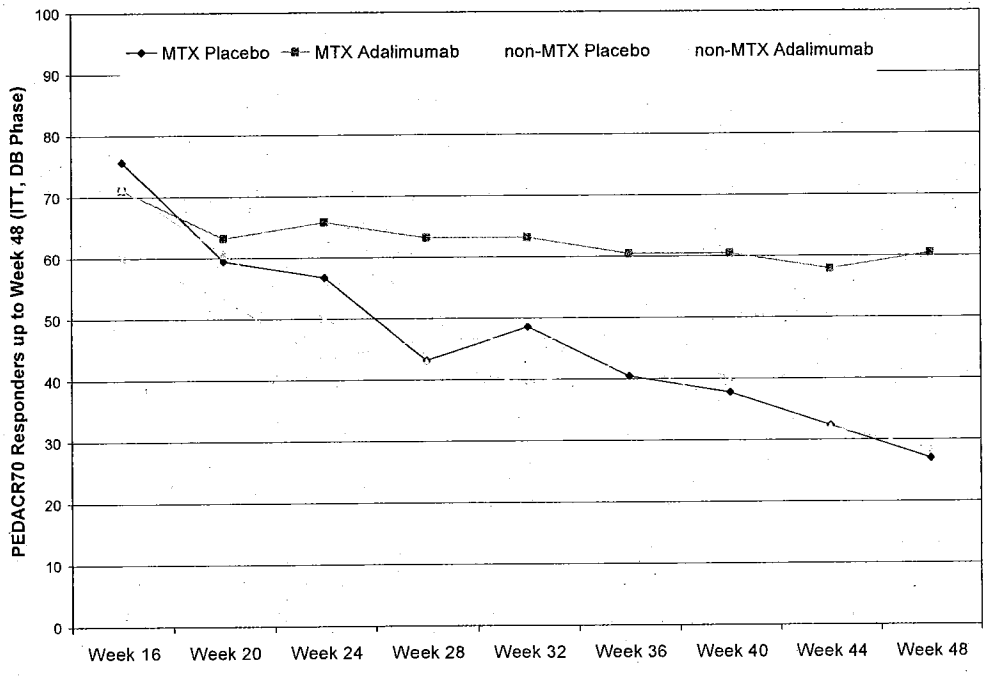
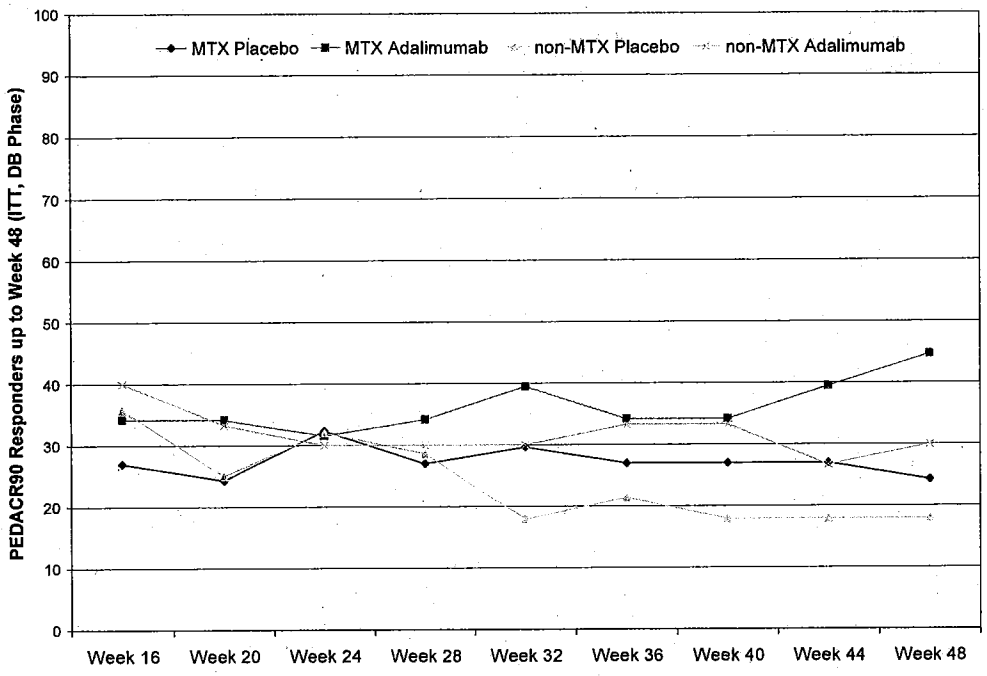


Figure 8: PEDACR90 Response by Stratification and Treatment Group for the DB Phase



2. The proportion of subjects with a PedACR30/50/70/90 response in the Open-Label Extension and Fixed Dose Phase

As noted by the Applicant, all subjects who completed 32 weeks of DB phase or experienced a flare were eligible to receive OL adalimumab during the OLE BSA phase. The Applicant presented the observed PedACR30 response during the OLE BSA phase by stratification and treatment assignment (during the DB phase). Data were presented as observed over the period of time that subjects received OLE BSA adalimumab (Appendix 2). Subjects with missing values but were present during the study phase were excluded in the denominator. Baseline value refers to the last observed value before the first dose of OLE BSA adalimumab. Because subjects entered the OLE BSA phase at different times depending on whether they experienced a flare during the DB treatment phase and subsequently entered the OLE FD phase at different times due to the timing of IRB approvals for the FD amendment, subjects had different duration of exposure during the OLE BSA phase. As a result, the number of subjects with exposure to adalimumab during the OLE BSA phase varies by OLE BSA visit and includes only five subjects with exposure of 136 weeks. This accounts for the apparent drop in response at some time points beyond Week 56 of OLE BSA exposure. More than half of the subjects entered the OLE BSA phase had duration of 72 weeks of treatment during this phase of the study.

In the filing communication letter dated July 9, 2007, we requested some information from the Applicant. One of the requests was on the PEDACR30/50/70/90 responses in the OLE BSA phase. In the letter, we stated that

> Tables 53, 54, 55 and 56 (not shown here) in the study report show efficacy analysis based on the proportions of PedACR 30/50/70/90 responses. The numerator for these proportions indicates the

number of ACR responders of those who came to the clinic at each particular visit. The footnotes in those tables state that for each visit the denominator value is "N2=number of subjects with non-missing responses," which reflect the number of all subjects who showed up for a particular visit. The result of this type of analysis is difficult to interpret because it is restricted to those subjects who showed up for those specific study visits. Provide an additional analysis of the data from the OLE-BSA phase of the study that includes a value for each subject who is still participating in the study at each time point, as follows:

a) For each subject, determine the duration of their participation in the OLE – BSA phase of the study. For example, if a subject participated in the OLE – BSA phase for 88 weeks, the subject should be counted as a study participant for every visit from the OLE-BSA baseline to Week 88 (inclusive) until the time of discontinuation. If the same subject missed any study visits between Weeks 0 and 88, the subject should still be counted as a participant of the study for the missing visits.

b) For each time point (study visit), analyze the proportion of subjects with PedACR 30/50/70/90 responses among the population of subjects still participating in the study at that time point (study visit). For subjects with missing PedACR response data at a given time point, but who were still participating in the study at that time point, impute the missing data using a suitable imputation technique; for example, last observation carried forward (LOCF). Your analysis should also specify the amount of missing data imputed for each time point.

Present the data in the same format as in Tables 53 to 56 with columns indicating treatment regimens (prior randomization in DB phase).

Based on the request, the Applicant provided new tables for the PEDACR30/50/70/90 (Appendix 3). As per consultation with Dr. Lapteva, we decided to re-analyze the data by using the observed responses in the numerator (same as the original in the CSR) and use all subjects still participating in the study at that time point as the denominator (LOCF approach), regardless of whether they have missed visits.

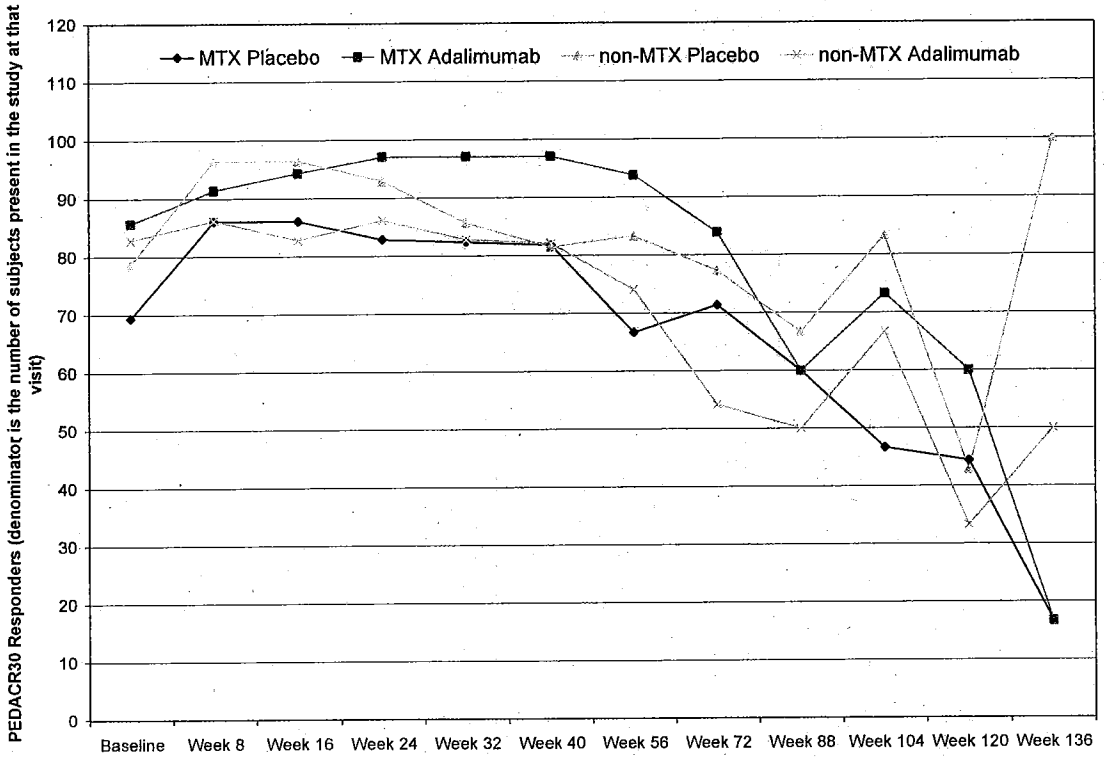
In the new analysis, the proportion of subjects with a PedACR30 response increased by Week 8 of OLE BSA from the last value of the DB phase in those subjects that received placebo during the DB phase (Table 10). On the other hand, in those subjects that received adalimumab during the DB phase, the proportion of subjects achieving a PedACR30 response by Week 8 of OLE BSA was similar to the response at the last value of the DB phase. This was expected given that unlike the placebo group, subjects were already being treated with adalimumab before receiving OLE BSA adalimumab. However, it could be noticed from the graph that there was a decreasing trend in the proportion of responders after Week 56 (Figure 9). The Applicant attributed the apparent decrease in the proportion of responders beyond Week 56 to the decrease in OLE BSA subjects at these time points than to true loss in response. Furthermore, there is also an increase in the number of missed visits beyond Week 56. Nonetheless, there is evidence that a high percentage of PedACR30 responders that received adalimumab or placebo during the DB were maintained during the OLE BSA phase up to Week 56 and possibly up to Week 72.

Table 10: PedACR30 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

	MTX				Non-MTX				Overall			
	Adalimumab (Placebo during DB phase) N=36		Adalimumab N=35		Adalimumab (Placebo during DB Phase) N=28		Adalimumab N=29		Adalimumab (Placebo during DB Phase) N=64		Adalimumab N=64	
Visit	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3
OLE BSA Baseline	25/36 (69.4)	3	30/35 (85.7)	1	22/28 (78.6)	1	24/29 (82.8)	3	47/64 (73.4)	4	54/64 (84.4)	4
Week 8	31/36 (86.1)	5	32/35 (91.4)	1	27/28 (96.4)	1	25/29 (86.2)	3	58/64 (90.6)	6	57/64 (89.1)	4
Week 16	31/36 (86.1)	5	33/35 (94.3)	1	27/28 (96.4)	1	24/29 (82.8)	4	58/64 (90.6)	6	57/64 (89.1)	5
Week 24	29/35 (82.9)	5	34/35 (97.1)	1	26/28 (92.9)	1	25/29 (86.2)	3	55/63 (87.3)	6	59/64 (92.2)	4
Week 32	28/34 (82.4)	4	34/35 (97.1)	1	24/28 (85.7)	3	24/29 (82.8)	5	52/62 (83.9)	7	58/64 (90.6)	6
Week 40	27/33 (81.8)	6	34/35 (97.1)	0	22/27 (81.5)	4	23/28 (82.1)	5	49/60 (81.7)	10	57/63 (90.5)	5
Week 56	20/30 (66.7)	6	30/32 (93.8)	1	20/24 (83.3)	3	20/27 (74.1)	7	40/54 (74.1)	9	50/59 (84.7)	8
Week 72	20/28 (71.4)	5	26/31 (83.9)	4	17/22 (77.3)	3	13/24 (54.2)	11	37/50 (74.0)	8	39/55 (70.9)	15
Week 88	15/25 (60.0)	9	15/25 (60.0)	9	12/18 (66.7)	6	8/16 (50.0)	7	27/43 (62.8)	15	23/41 (56.1)	16
Week 104	7/15 (46.7)	7	11/15 (73.3)	4	10/12 (83.3)	2	6/9 (66.7)	2	17/27 (63.0)	9	17/24 (70.8)	6
Week 120	4/9 (44.4)	4	6/10 (60.0)	4	3/7 (42.9)	4	2/6 (33.3)	3	7/16 (43.8)	8	8/16 (50.0)	7
Week 136	1/6 (16.7)	5	1/6 (16.7)	5	1/1 (100.0)	0	1/2 (50.0)	0	2/7 (28.6)	5	2/8 (25.0)	5

N1 = number of responders (no LOCF)
N2 = number of subjects present in the study at that visit
N3= number of subjects with missing values, but present in study phase.

Figure 9: PedACR30 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)



Like PEDACR30 responders, the proportion of subjects with a PedACR50/70/90 showed similar response trends (Table 11 - Table 13 and Figure 10 - Figure 12). The Tables and Figures showed similar increase in the proportion of subjects achieving a PEDACR50/70/90 response at Week 8 of OLE BSA compared to the last observed value of the DB phase. In addition, responses are maintained during the OLE BSA phase at least up to Week 56 or Week 72. According to the Applicant, the decrease in the number of subjects with OLE BSA visits over the 136 weeks can be attributed to differences in timing of when subjects began and completed OLE BSA treatment such that the responses beyond Week 56 represent a subset of subjects that entered the OLE BSA phase. Therefore, any apparent decrease in the proportion of responders beyond Week 56 has more to do with the decrease in OLE BSA subjects at these time points than a true loss in response.

Table 11: PedACR50 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

	MTX				Non-MTX				Overall			
	Adalimumab (Placebo during DB phase) N=36		Adalimumab N=35		Adalimumab (Placebo during DB Phase) N=28		Adalimumab N=29		Adalimumab (Placebo during DB Phase) N=64		Adalimumab N=64	
Visit	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3
OLE BSA Baseline	20/36 (55.6)	3	27/35 (77.1)	1	19/28 (67.9)	1	22/29 (75.9)	3	39/64 (60.9)	4	49/64 (76.6)	4
Week 8	27/36 (75.0)	5	32/35 (91.4)	1	26/28 (92.9)	1	24/29 (82.8)	3	53/64 (82.8)	6	56/64 (87.5)	4
Week 16	30/36 (83.3)	5	31/35 (88.6)	1	25/28 (89.3)	1	23/29 (79.3)	4	55/64 (85.9)	6	54/64 (84.4)	5
Week 24	27/35 (77.1)	5	32/35 (91.4)	1	25/28 (89.3)	1	25/29 (86.2)	3	52/63 (82.5)	6	57/64 (89.1)	4
Week 32	27/34 (79.4)	4	34/35 (97.1)	1	23/28 (82.1)	3	24/29 (82.8)	5	50/62 (80.6)	7	58/64 (90.6)	6
Week 40	27/33 (81.8)	6	33/35 (94.3)	0	22/27 (81.5)	4	23/28 (82.1)	5	49/60 (81.7)	10	56/63 (88.9)	5
Week 56	20/30 (66.7)	6	29/32 (90.6)	1	20/24 (83.3)	3	20/27 (74.1)	7	40/54 (74.1)	9	49/59 (83.1)	8
Week 72	19/28 (67.9)	5	25/31 (80.6)	4	16/22 (72.7)	3	13/24 (54.2)	11	35/50 (70.0)	8	38/55 (69.1)	15
Week 88	14/25 (56.0)	9	13/25 (52.0)	9	12/18 (66.7)	6	8/16 (50.0)	7	26/43 (60.5)	15	21/41 (51.2)	16
Week 104	6/15 (40.0)	7	10/15 (66.7)	4	10/12 (83.3)	2	6/9 (66.7)	2	16/27 (59.3)	9	16/24 (66.7)	6
Week 120	4/9 (44.4)	4	6/10 (60.0)	4	3/7 (42.9)	4	2/6 (33.3)	3	7/16 (43.8)	8	8/16 (50.0)	7
Week 136	1/6 (16.7)	5	0/6 (0.0)	5	1/1 (100.0)	0	½ (50.0)	0	2/7 (28.6)	5	1/8 (12.5)	5

N1 = number of responders (no LOCF)
N2 = number of subjects present in the study at that visit
N3= number of subjects with missing values, but present in study phase.

Figure 10: PedACR50 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

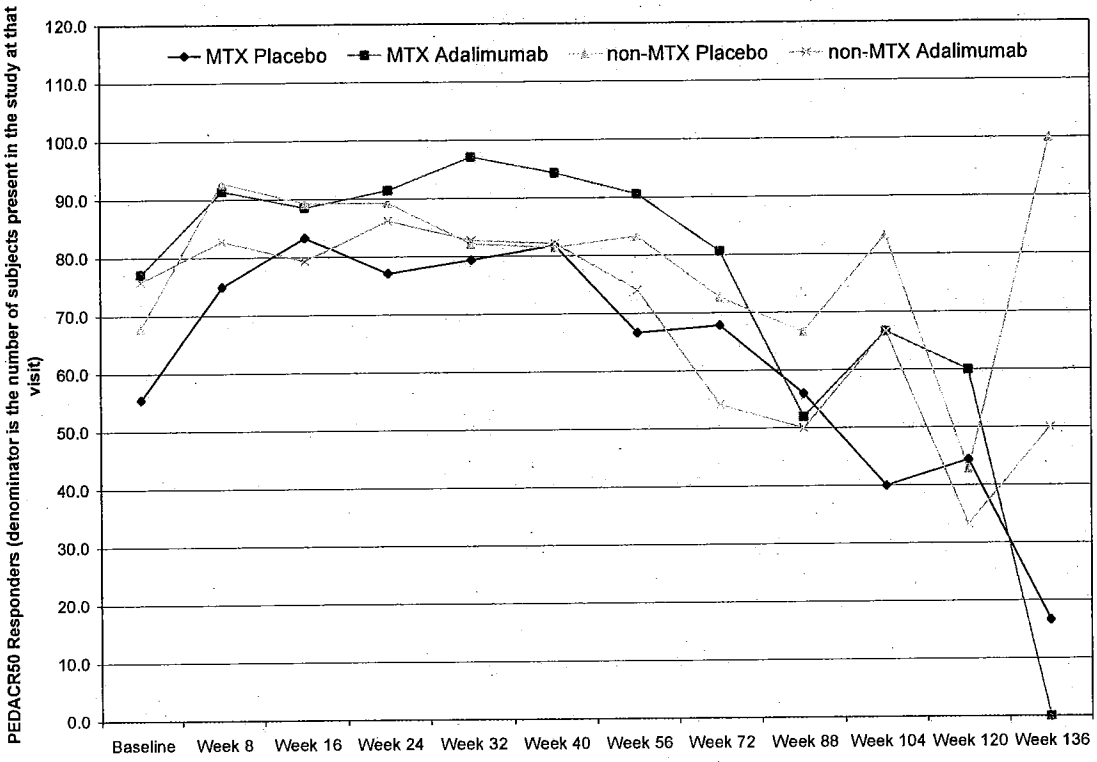


Table 12: PedACR70 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

	MTX				Non-MTX				Overall			
	Adalimumab (Placebo during DB phase) N=36		Adalimumab N=35		Adalimumab (Placebo during DB Phase) N=28		Adalimumab N=29		Adalimumab (Placebo during DB Phase) N=64		Adalimumab N=64	
Visit	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3
OLE BSA Baseline	12/36 (33.3)	3	23/35 (65.7)	1	13/28 (46.4)	1	17/29 (58.6)	3	25/64 (39.1)	4	40/64 (62.5)	4
Week 8	19/36 (52.8)	5	26/35 (74.3)	1	22/28 (78.6)	1	20/29 (69.0)	3	41/64 (64.1)	6	46/64 (71.9)	4
Week 16	23/36 (63.9)	5	31/35 (88.6)	1	19/28 (67.9)	1	17/29 (58.6)	4	42/64 (65.6)	6	48/64 (75.0)	5
Week 24	23/35 (65.7)	5	29/35 (82.9)	1	20/28 (71.4)	1	22/29 (75.9)	3	43/63 (68.3)	6	51/64 (79.7)	4
Week 32	23/34 (67.6)	4	29/35 (82.9)	1	19/28 (67.9)	3	22/29 (75.9)	5	42/62 (67.7)	7	51/64 (79.7)	6
Week 40	22/33 (66.7)	6	32/35 (91.4)	0	17/27 (63.0)	4	23/28 (82.1)	5	39/60 (65.0)	10	55/63 (87.3)	5
Week 56	18/30 (60.0)	6	25/32 (78.1)	1	16/24 (66.7)	3	19/27 (70.4)	7	34/54 (63.0)	9	44/59 (74.6)	8
Week 72	16/28 (57.1)	5	23/31 (74.2)	4	16/22 (72.7)	3	13/24 (54.2)	11	32/50 (64.0)	8	36/55 (65.5)	15
Week 88	12/25 (48.0)	9	13/25 (52.0)	9	12/18 (66.7)	6	8/16 (50.0)	7	24/43 (55.8)	15	21/41 (51.2)	16
Week 104	4/15 (26.7)	7	10/15 (66.7)	4	9/12 (75.0)	2	5/9 (55.6)	2	13/27 (48.1)	9	15/24 (62.5)	6
Week 120	4/9 (44.4)	4	5/10 (50.0)	4	3/7 (42.9)	4	2/6 (33.3)	3	7/16 (43.8)	8	7/16 (43.8)	7
Week 136	1/6 (16.7)	5	0/6 (0.0)	5	0/1 (0.0)	0	½ (50.0)	0	1/7 (14.3)	5	1/8 (12.5)	5

N1 = number of responders (no LOCF)
N2 = number of subjects present in the study at that visit
N3= number of subjects with missing values, but present in study phase.

Figure 11: PedACR70 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

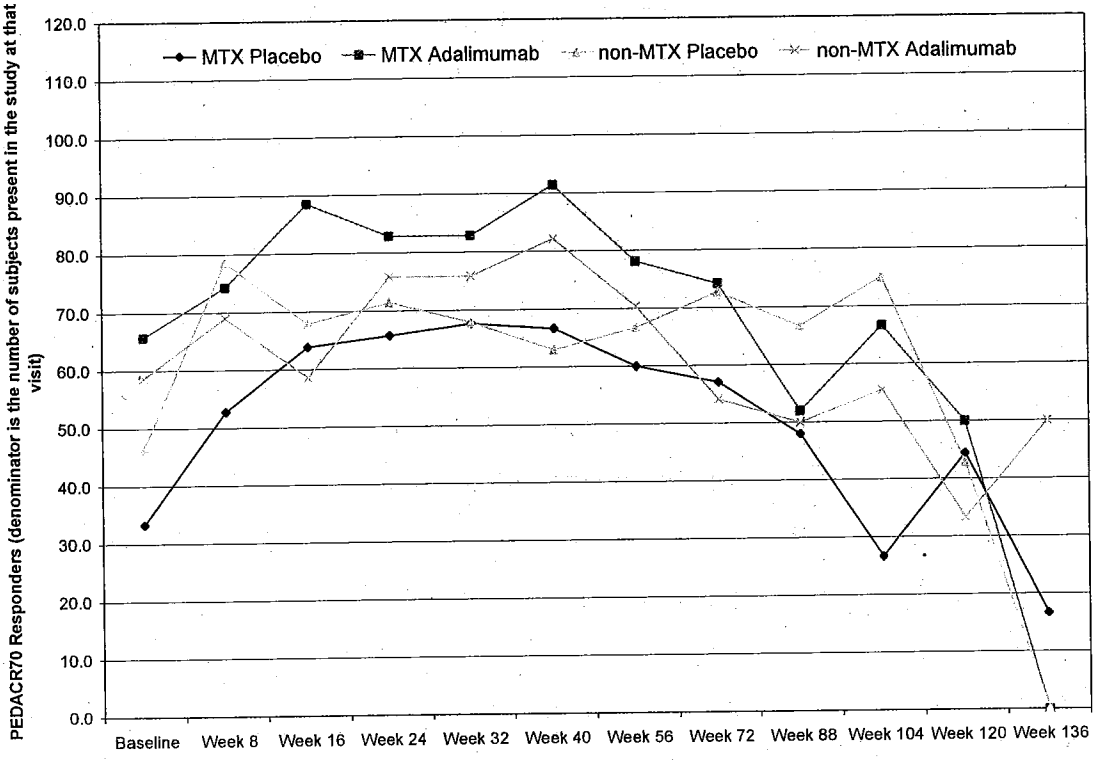
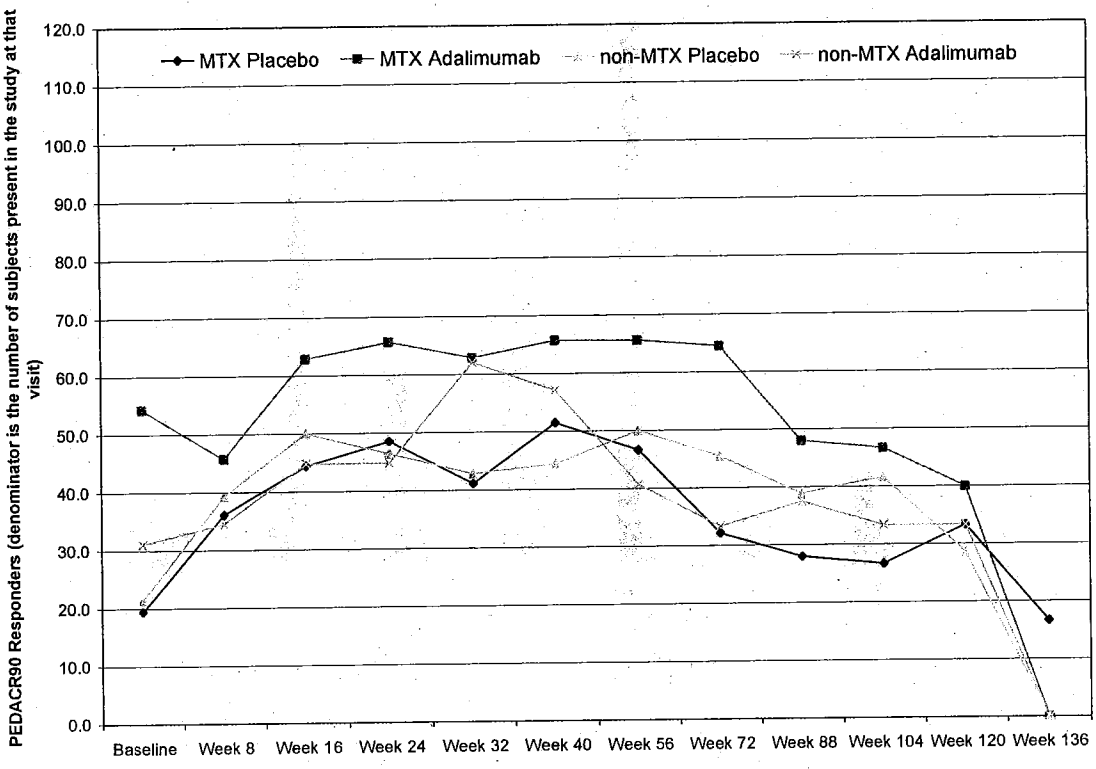


Table 13: PedACR90 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

	MTX				Non-MTX				Overall			
	Adalimumab (Placebo during DB phase) N=36		Adalimumab N=35		Adalimumab (Placebo during DB Phase) N=28		Adalimumab N=29		Adalimumab (Placebo during DB Phase) N=64		Adalimumab N=64	
Visit	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3	N1/N2(%)	N3
OLE BSA Baseline	7/36 (19.4)	3	19/35 (54.3)	1	6/28 (21.4)	1	9/29 (31.0)	3	13/64 (20.3)	4	28/64 (43.8)	4
Week 8	13/36 (36.1)	5	16/35 (45.7)	1	11/28 (39.3)	1	10/29 (34.5)	3	24/64 (37.5)	6	26/64 (40.6)	4
Week 16	16/36 (44.4)	5	22/35 (62.9)	1	14/28 (50.0)	1	13/29 (44.8)	4	30/64 (46.9)	6	35/64 (54.7)	5
Week 24	17/35 (48.6)	5	23/35 (65.7)	1	13/28 (46.4)	1	13/29 (44.8)	3	30/63 (47.6)	6	36/64 (56.3)	4
Week 32	14/34 (41.2)	4	22/35 (62.9)	1	12/28 (42.9)	3	18/29 (62.1)	5	26/62 (41.9)	7	40/64 (62.5)	6
Week 40	17/33 (51.5)	6	23/35 (65.7)	0	12/27 (44.4)	4	16/28 (57.1)	5	29/60 (48.3)	10	39/63 (61.9)	5
Week 56	14/30 (46.7)	6	21/32 (65.6)	1	12/24 (50.0)	3	11/27 (40.7)	7	26/54 (48.1)	9	32/59 (54.2)	8
Week 72	9/28 (32.1)	5	20/31 (64.5)	4	10/22 (45.5)	3	8/24 (33.3)	11	19/50 (38.0)	8	28/55 (50.9)	15
Week 88	8/25 (28.0)	9	12/25 (48.0)	9	7/18 (38.9)	6	6/16 (37.5)	7	14/43 (32.6)	15	18/41 (43.9)	16
Week 104	4/15 (26.7)	7	7/15 (46.7)	4	5/12 (41.7)	2	3/9 (33.3)	2	9/27 (33.3)	9	10/24 (41.7)	6
Week 120	3/9 (33.3)	4	4/10 (40.0)	4	2/7 (28.6)	4	2/6 (33.3)	3	5/16 (31.3)	8	6/16 (37.5)	7
Week 136	1/6 (16.7)	5	0/6 (0.0)	5	0/1 (0.0)	0	0/2 (0.0)	0	1/7 (14.3)	5	0/8 (0.0)	5

N1 = number of responders (no LOCF)
N2 = number of subjects present in the study at that visit
N3= number of subjects with missing values, but present in study phase.

Figure 12: PedACR90 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)



3. The proportion of subjects with a PedACR30/50/70/90 response in the Open-label Extension Fixed Dose Phase

As stated before, the decrease in the number of subjects with OLE BSA visits over the 136 weeks can be attributed to differences in timing of when subjects began and completed OLE BSA treatment. As an example, most subjects in the MTX with dose-increased group who are PEDACR30 responders completed the OLE BSA at around Week 72, while most subjects in the non-MTX with dose increased completed at Week 56. In contrast, most subjects whose dose remained the same or decreased who are PEDACR30 responders completed later (i.e. Week 104 for non-MTX and week 120 for MTX group), see Figure 13.

The graph in Figure 14 demonstrates that subjects maintained their PEDACR responses during the 16 weeks of OLE FD treatment regardless of their MTX status or whether they increased or decreased/stayed at the same dose. Note that the Week 0 data represents the last observed PEDACR response before first dose of fixed dose adalimumab.

Figure 13: Proportion of PEDACR30 responders by Last Assessment Week of OLE BSA before OLE FD

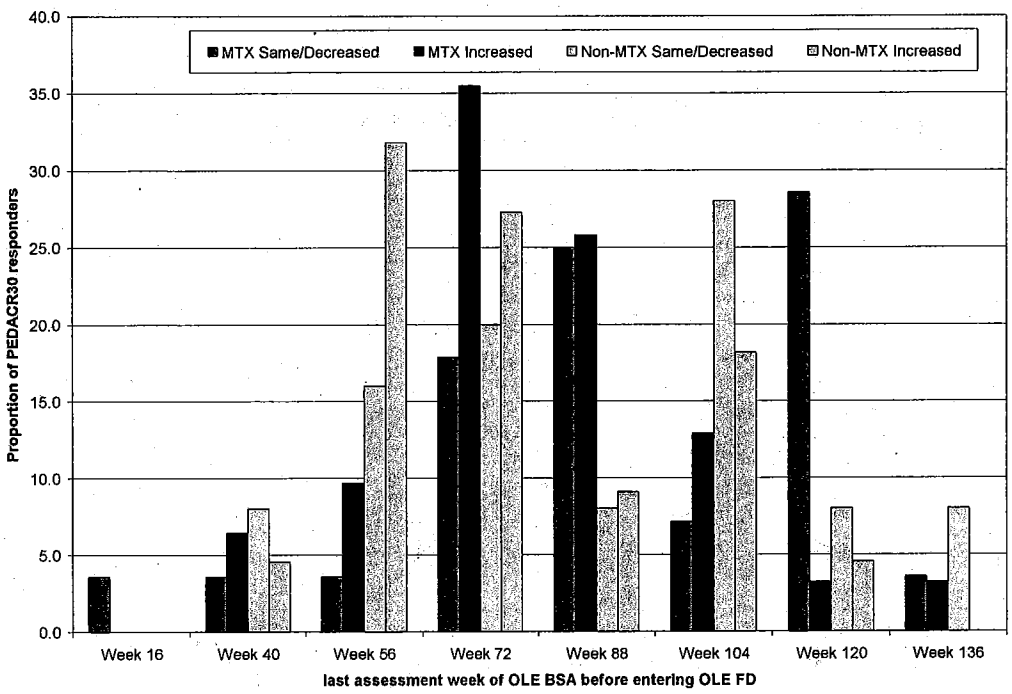
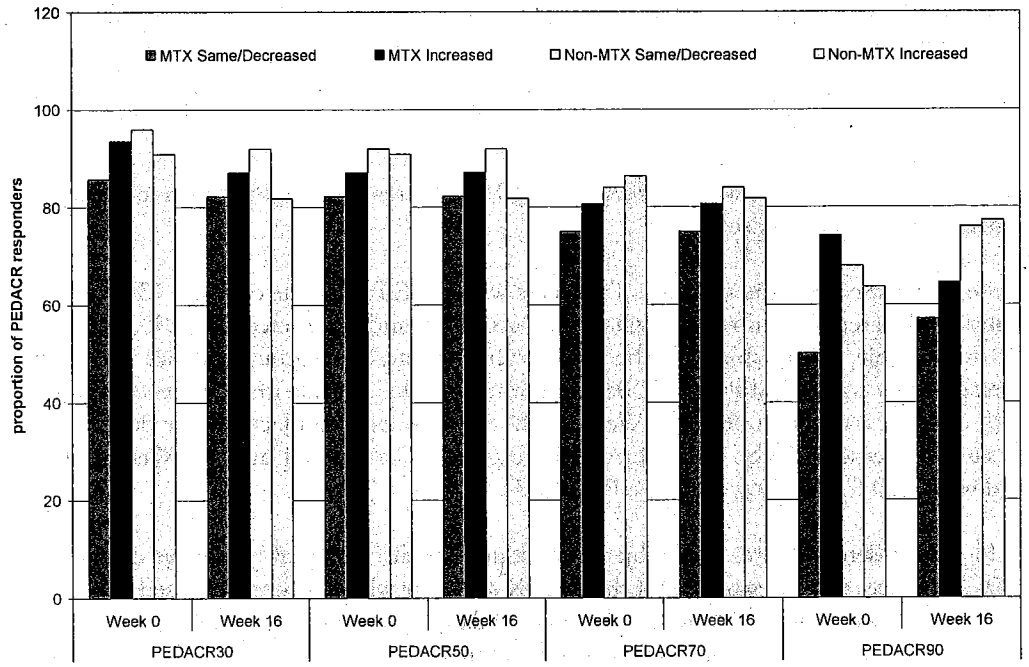


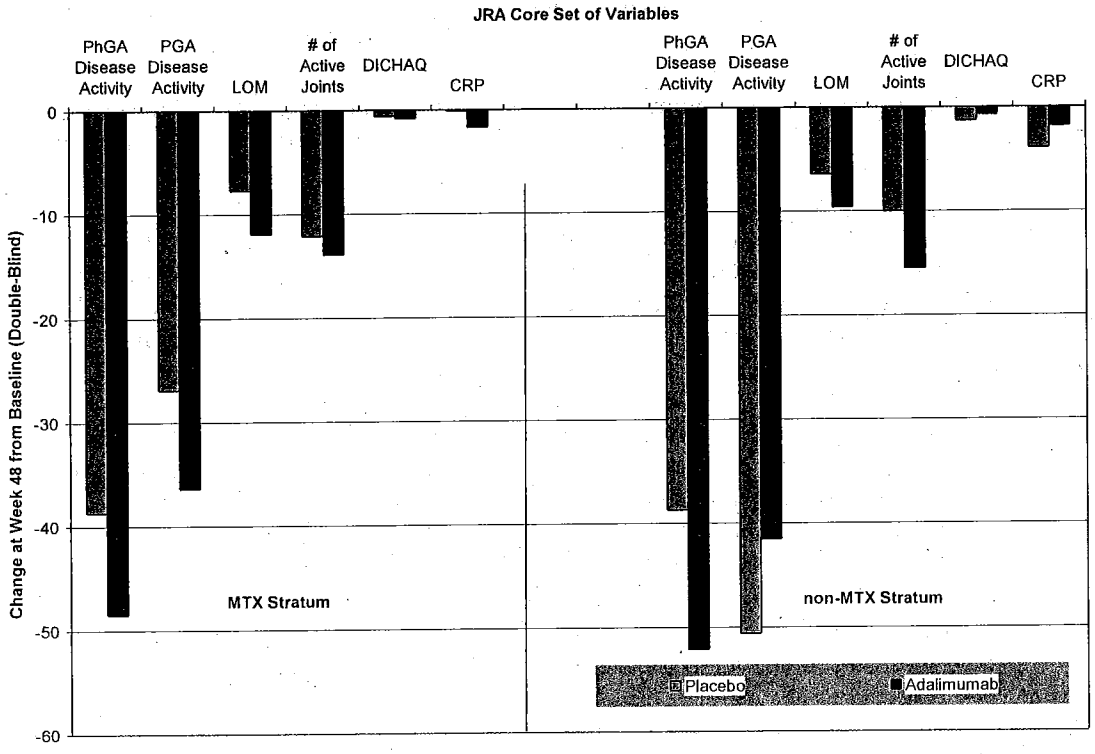
Figure 14: Proportion of PEDACR30/50/70/90 responders at the OLE FD phase



4. JRA Core set of variables

The change from open-label lead-in baseline for the individual JRA core set of variables at Week 48 is presented in Figure 15. In the MTX stratum, the results of the individual JRA core set of variables supports the decrease in disease flare, as well as increase in the proportion of PEDACR responders in the adalimumab-treated groups as demonstrated by the greater improvement of each individual JRA components compared to placebo. Like the MTX stratum, there is also evidence of greater improvement in most JRA components in the adalimumab-treated group compared to placebo in the non-MTX stratum. Thus, the results of the individual JRA core set variables support the clinical benefit of adalimumab in JRA subjects as already demonstrated by the decrease in the number of disease flares compared to placebo in the non-MTX stratum and the delay of the onset of disease flare in both MTX strata, as well as the increase in the proportion of PEDACR responders compared to placebo in both MTX strata.

Figure 15: Change from Open-label Lead-in Baseline for the Juvenile Rheumatoid Arthritis Core Set of Variables at Week 48 (ITT Population, DB Phase)



*Negative change from baseline implies improvement.

3.1.3.3 Summary of Efficacy Results

In summary, adalimumab demonstrated efficacy in subjects with JRA as follows:

In the Open-label Lead-in Phase:

- At Week 16, I find that (82%) subjects were PedACR30 responders: 78 (92%) subjects in the MTX stratum and 63 (73%) subjects in the non-MTX stratum.

In the Double-blind Phase:

- The primary efficacy endpoint was the proportion of of adalimumab-treated subjects in the non-MTX stratum who experienced disease flare in the DB phase. A statistically significant lower proportion of adalimumab-treated subjects (71%) demonstrated disease flare compared to placebo-treated subjects (43%) in the non-MTX stratum (p=0.031). The result was not affected when different imputation strategies were applied to handle missing data.

- The following are results from protocol-defined secondary endpoints. Note that the Applicant did not apply any multiplicity adjustments to the statistical tests performed on these secondary endpoints.

    - Like the non-MTX stratum, lower proportion of adalimumab-treated subjects (65%) demonstrated disease flare compared to placebo-treated subjects (37%) in the MTX stratum.

    - There is evidence that adalimumab was superior in delaying the onset of disease flare compared to placebo in the non-MTX stratum. Median time to disease flare from the first dose of DB treatment was more than 32 weeks for subjects in the adalimumab treatment group and about 14 weeks for subjects who received placebo.

    - There is also evidence that adalimumab was superior in delaying the onset of disease flare compared to placebo in the MTX stratum. Median time to disease flare from the first dose of DB treatment was greater than 32 weeks for subjects receiving adalimumab and about 20 weeks for subjects receiving placebo.

    - Meanwhile, there is evidence that a greater proportion of subjects who received adalimumab in the MTX and the non-MTX stratum were PedACR30/50/70 responders compared to subjects who received placebo at Week 48.

In the Open-label Extension Body Surface Area phase:

- The proportion of subjects with a PedACR30/50/70/90 response increased by Week 8 of OLE BSA from the last value of the DB phase (i.e. OLE BSA baseline) in those subjects that received placebo during the DB phase and the high response rate was maintained during the OLE BSA phase (e.g. from 73% at OLE BSA baseline to 91% of subjects at Week 8 with PedACR30 response).

- Meanwhile, in those subjects that received adalimumab during the DB phase, the proportion of subjects achieving a PedACR 30 response by Week 8 of OLE BSA was almost similar to

the response at the last value of the DB phase (i.e. OLE BSA baseline) and was maintained during the OLE BSA phase.

In the Open-label Extension Fixed Dose phase:

- Subjects maintained PedACR responses during the 16 weeks of OLE FD treatment regardless of whether they remained on the same dose/decreased dose or increased dose administered compared to the dose received during the OLE BSA phase.

3.2 EVALUATION OF SAFETY

Dr. Lapteva reviewed the safety of adalimumab in detail. The reader is referred to Dr. Lapteva's review for information regarding the adverse event profile

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

Subgroup analyses of sex, age and gender, as well as on JRA duration, body mass index, weight, and C-reactive protein (CRP) range were conducted separately according to the primary endpoint (i.e. disease flare). A logistic regression analysis (using the primary imputation approach) that includes the interaction term was conducted at the end of the double-blind phase (i.e. Week 48) to explore the relationship between the subgroups (which is based on open-label lead-in baseline) and treatment.

As stated in 3.1.2, there were 133 subjects who were randomized into the DB phase. The majority of the subjects who participated were white, female and had an approximate mean age of 11 years at the open-label lead-in. Because of the small numbers of males and of nonwhites in the study, any claims of parity in terms of patient's sex or race are essentially unsupported. The mean body weight and mean body mass index are almost the same in both strata (body weight is approximately 43 kg and BMI is approximately 19). Meanwhile, the duration of JRA is slightly longer in the MTX group (approximately 4 years) compared to the non-MTX group (approximately 3 years). However, the duration of JRA is almost the same between the adalimumab group and the placebo group within each stratum. Like the duration of JRA, there is slightly greater proportion of subjects in the MTX stratum (41%) who have normal CRP compared to the non-MTX stratum (33%). Also, in the non-MTX stratum, it appears that higher proportion of subject in the adalimumab group (40%) has normal CRP compared to the placebo group (25%).

In the analyses of subgroups, there were no remarkable effects of age, gender, race or any of the baseline disease characteristics analyzed here in both MTX strata (i.e. JRA duration, CRP range, and body mass index) according to the primary endpoint analysis. Because nearly all subjects in each study were young, white, and female, it is impossible to distinguish the possible treatment effects for the subgroups of race, BMI, or sex (Table 14).

There might be an effect of weight on the proportion of subjects experiencing disease flares up to Week 48 in the non-MTX strata. Higher proportion of subjects in the placebo group who are less than 40 kg experienced disease flare compared to the proportion of subjects in the Adalimumab

group. However, because of the small number of subjects within each subgroup, this limited the ability to precisely estimate the treatment effect in the subpopulation.

Table 14: Primary Analysis of Disease Flare Up to Week 48 by Subgroup Defined at Open-Label Baseline (ITT population, Double-Blind Phase, Non-MTX Group)

Analysis	Non-MTX		MTX	
	Adalimumab N=30	Adalimumab N=30	Placebo N=28	Placebo N=28
Age				
4 – 8 years (N=16)	2/8 (25%)	2/6 (33%)	7/12 (58%)	6/8 (75%)
9 – 12 years (N=17)	5/10 (50%)	6/17 (35%)	8/10 (80%)	6/7 (86%)
13 – 17 years (N=25)	6/12 (50%)	6/15 (40%)	9/15 (60%)	8/13 (62%)
Gender				
Female (N=43)	11/23 (48%)	12/30 (40%)	19/30 (63%)	14/20 (70%)
Male (N=15)	2/7 (29%)	2/8 (25%)	5/7 (71%)	6/8 (75%)
Race				
White (N=53)	11/26 (42%)	12/36 (33%)	24/36 (67%)	19/27 (70%)
Non-white (N=5)	2/3 (67%)	1/1 (100%)	0/1 (0%)	1/1 (100%)
JRA Duration				
≤1 year (N=22)	3/9 (33%)	3/8 (38%)	2/7 (29%)	6/13 (46%)
>1 to ≤2 years (N=8)	2/6 (33%)	0/7 (0%)	6/8 (75%)	2/2 (100%)
>2 to ≤4 years (N=12)	4/7 (57%)	3/9 (33%)	3/5 (60%)	4/5 (80%)
>4 to ≤8 years (N=10)	2/4 (50%)	2/6 (33%)	9/12 (75%)	6/6 (100%)
> 8 years (N=6)	2/4 (50%)	6/8 (75%)	4/5 (80%)	2/2 (100%)
CRP Range				
Normal (N=19)	5/12 (42%)	5/14 (36%)	8/16 (50%)	4/7 (53%)
Abnormal (N=39)	8/18 (44%)	9/24 (38%)	14/20 (70%)	16/21 (76%)
Weight				
< 40 kg (N=27)	4/13 (31%)	7/18 (39%)	12/17 (71%)	12/14 (86%)
≥ 40 kg (N=31)	9/17 (53%)	7/20 (35%)	12/20 (60%)	8/14 (57%)
BMI				
< 25 normal (N=48)	10/26 (38%)	11/33 (33%)	19/28 (68%)	15/22 (68%)
≥ 25 to <30 overweight (N=6)	2/3 (67%)	2/4 (50%)	5/7 (71%)	3/3 (100%)
≥ 30 obese (N=4)	1/1 (100%)	1/1 (100%)	0/2 (0%)	2/3 (67%)

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

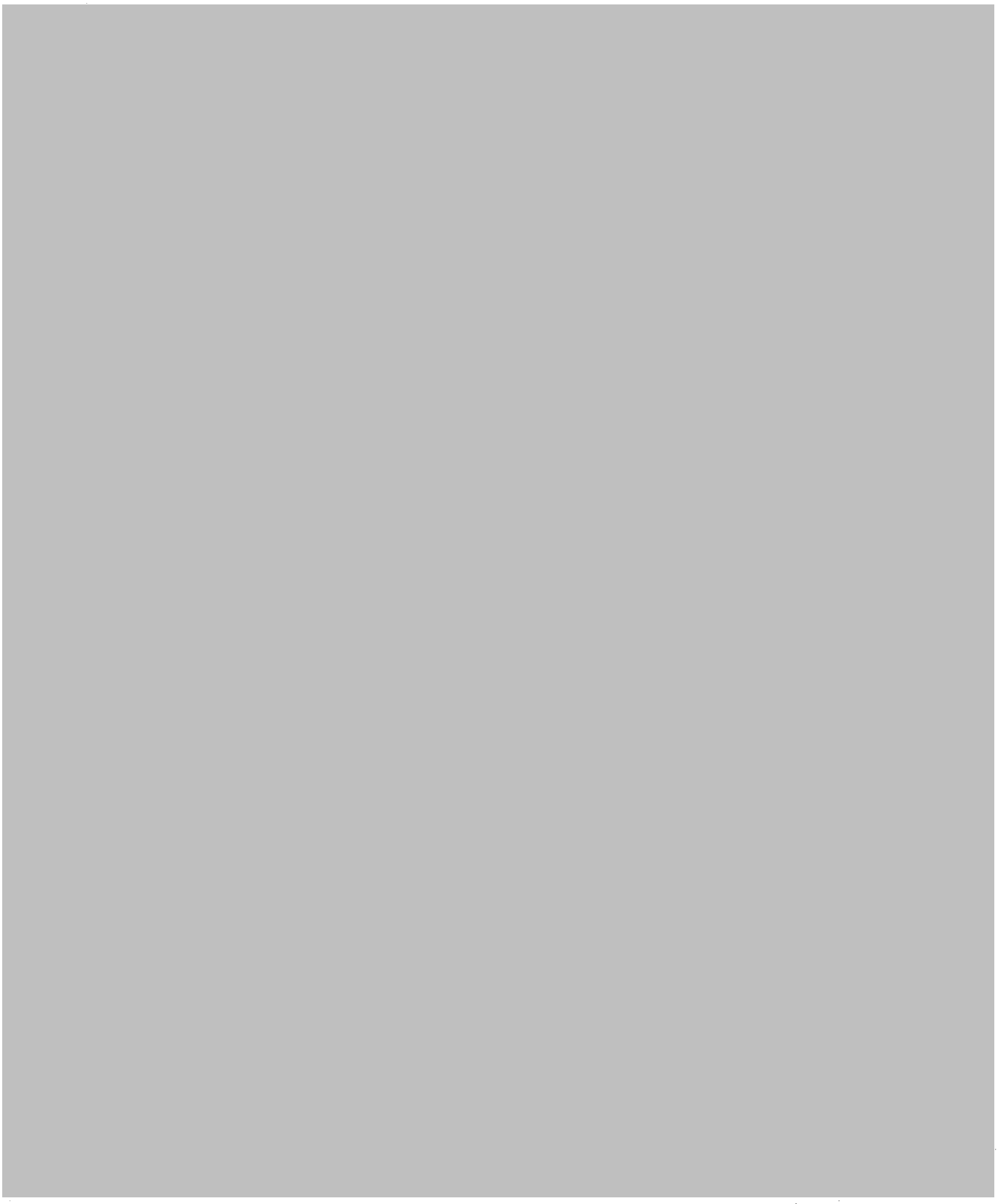
There are no major statistical issues in this sBLA submission that could not be handled by recoding and re-analyzing the data. There were few discrepancies found in the results provided in the study report and after re-analyses of the data. However, these discrepancies did not alter or affect the overall efficacy conclusion of adalimumab as a treatment for juvenile RA in pediatric patients.

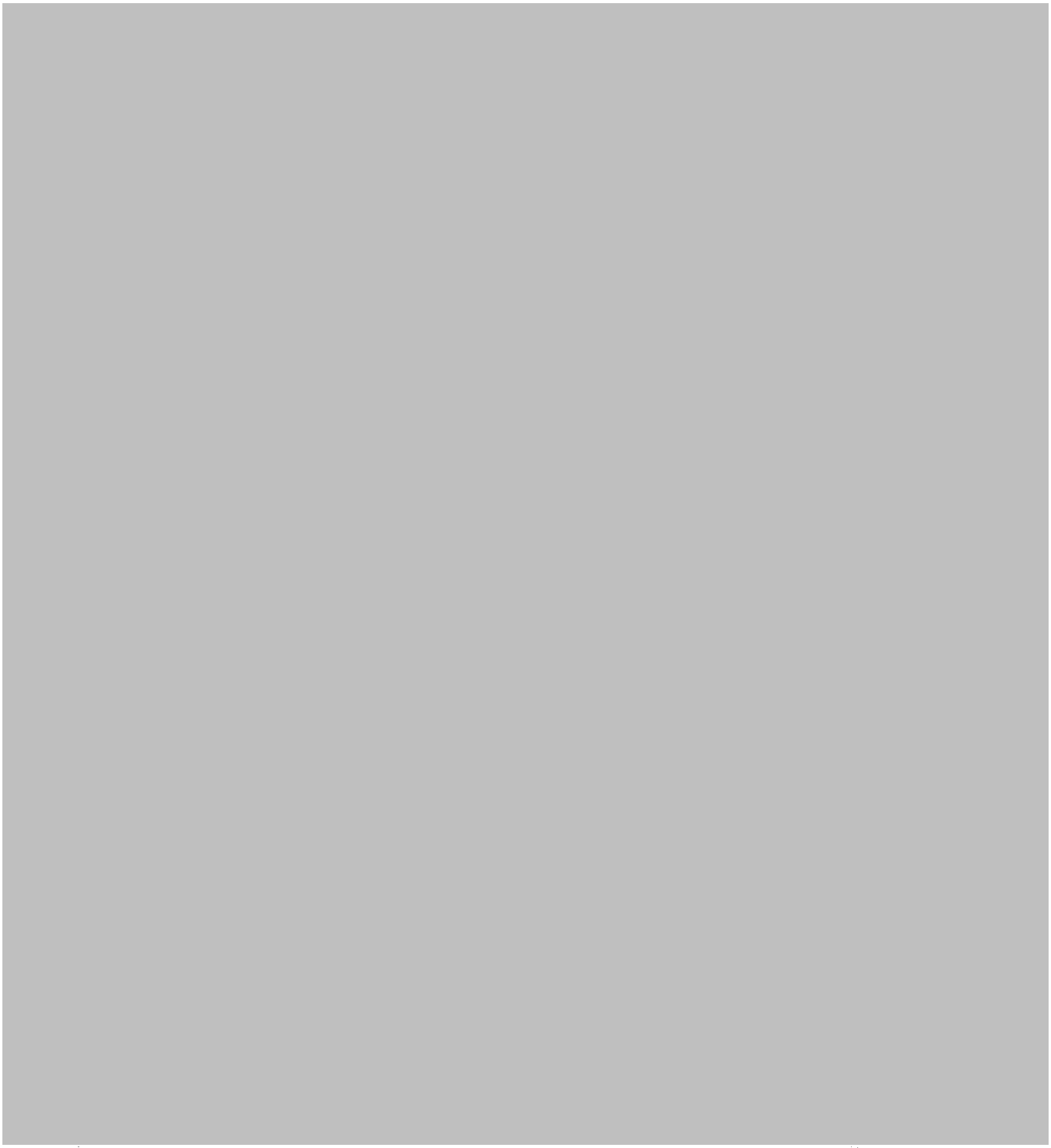
5.2 CONCLUSIONS AND RECOMMENDATIONS

The applicant, Abbott Laboratories., has proposed the use of adalimumab as a treatment for juvenile RA in pediatric patients. The primary claim of the applicant is that subjects with JRA who were administered adalimumab experienced less disease flares than did subjects who were administered placebo, regardless of their methotrexate (MTX) status.

The evidence taken from study DE038 reviewed indicated statistical support favoring the use of adalimumab as a treatment for juvenile RA in pediatric patients.

6 LABELLING





7 APPENDIX

Appendix 1

Table 45. PedACR30 Responders up to Week 48 (ITT Population, Double-blind Phase)

	MTX			non-MTX			Overall		
	Placebo N = 37	Adalimumab 24 mg/m^2 BSA eow N = 38		Placebo N = 28	Adalimumab 24 mg/m^2 BSA eow N = 30		Placebo N = 65	Adalimumab 24 mg/m^2 BSA eow N = 68	
Visit	n (%)		p-value[a,b]	n (%)		p-value[a,b]	n (%)		p-value[a,b]
Week 16	37 (100.0)	38 (100.0)	-	28 (100.0)	30 (100.0)	-	65 (100.0)	68 (100.0)	-
Week 20	33 (89.2)	37 (97.4)	0.200	25 (89.3)	28 (93.3)	0.665	58 (89.2)	65 (95.6)	0.200
Week 24	29 (78.4)	30 (78.9)	0.952	22 (78.6)	24 (80.0)	0.893	51 (78.5)	54 (79.4)	0.893
Week 28	24 (64.9)	26 (68.4)	0.744	19 (67.9)	23 (76.7)	0.453	43 (66.2)	49 (72.1)	0.461
Week 32	22 (59.5)	26 (68.4)	0.419	16 (57.1)	21 (70.0)	0.309	38 (58.5)	47 (69.1)	0.201
Week 36	18 (48.6)	24 (63.2)	0.206	13 (46.4)	20 (66.7)	0.120	31 (47.7)	44 (64.7)	0.048*
Week 40	16 (43.2)	24 (63.2)	0.084	12 (42.9)	19 (63.3)	0.118	28 (43.1)	43 (63.2)	0.020*
Week 44	16 (43.2)	24 (63.2)	0.084	10 (35.7)	18 (60.0)	0.064	26 (40.0)	42 (61.8)	0.012*
Week 48	14 (37.8)	24 (63.2)	0.028*	9 (32.1)	17 (56.7)	0.061	23 (35.4)	41 (60.3)	0.004**

BSA = body surface area

a. The p-value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's Exact test was used.

b. Statistically significant, ***p ≤ 0.001, **p ≤ 0.01, and *p ≤ 0.05.

Cross Reference: DE038 Section 14, Table 14.2__7.

PEDACR30	MTX	
	Placebo N=37	Adalimumab N=38
Reviewer's Week 48	15 (40.5)	23 (60.5)

Table 46. PedACR50 Responders up to Week 48 (ITT Population, Double-blind Phase)

	MTX			non-MTX			Overall		
	Placebo N = 37	Adalimumab 24 mg/m^2 BSA eow N = 38		Placebo N = 28	Adalimumab 24 mg/m^2 BSA eow N = 30		Placebo N = 65	Adalimumab 24 mg/m^2 BSA eow N = 68	
Visit	n (%)		p-value[a,b]	N (%)		p-value[a,b]	n (%)		p-value[a,b]
Week 16	35 (94.6)	37 (97.4)	0.615	26 (92.9)	25 (83.3)	0.425	61 (93.8)	62 (91.2)	0.745
Week 20	31 (83.8)	34 (89.5)	0.469	24 (85.7)	24 (80.0)	0.732	55 (84.6)	58 (85.3)	0.913
Week 24	29 (78.4)	30 (78.9)	0.952	21 (75.0)	20 (66.7)	0.486	50 (76.9)	50 (73.5)	0.651
Week 28	20 (54.1)	26 (68.4)	0.201	16 (57.1)	21 (70.0)	0.309	36 (55.4)	47 (69.1)	0.102
Week 32	20 (54.1)	25 (65.8)	0.300	16 (57.1)	19 (63.3)	0.630	36 (55.4)	44 (64.7)	0.272
Week 36	18 (48.6)	24 (63.2)	0.206	12 (42.9)	18 (60.0)	0.192	30 (46.2)	42 (61.8)	0.071
Week 40	15 (40.5)	24 (63.2)	0.050*	12 (42.9)	17 (56.7)	0.293	27 (41.5)	41 (60.3)	0.031*
Week 44	16 (43.2)	24 (63.2)	0.084	10 (35.7)	17 (56.7)	0.110	26 (40.0)	41 (60.3)	0.019*
Week 48	14 (37.8)	24 (63.2)	0.028*	9 (32.1)	16 (53.3)	0.103	23 (35.4)	40 (58.8)	0.007**

BSA = body surface area

a. The p-value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's Exact test was used.

b. Statistically significant, ***p ≤ 0.001, **p ≤ 0.01, and *p ≤ 0.05.

Cross Reference: DE038 Section 14, Table 14.2__8.

PEDACR50	MTX	
	Placebo N=37	Adalimumab N=38
Reviewer's Week 48	14 (37.8)	23 (60.5)

Table 47. PedACR70 Responders up to Week 48 (ITT Population, Double-blind Phase)

	MTX			non-MTX			Overall		
	Placebo N=37	Adalimumab 24 mg/m^2 BSA eow N=38		Placebo N=28	Adalimumab 24 mg/m^2 BSA eow N=30		Placebo N=65	Adalimumab 24 mg/m^2 BSA eow N=68	
Visit	n (%)		p-value[a,b]	n (%)		p-value[a,b]	n (%)		p-value[a,b]
Week 16	28 (75.7)	27 (71.1)	0.651	20 (71.4)	18 (60.0)	0.360	48 (73.8)	45 (66.2)	0.335
Week 20	22 (59.5)	24 (63.2)	0.742	17 (60.7)	16 (53.3)	0.571	39 (60.0)	40 (58.8)	0.890
Week 24	21 (56.8)	25 (65.8)	0.422	14 (50.0)	13 (43.3)	0.611	35 (53.8)	38 (55.9)	0.814
Week 28	16 (43.2)	24 (63.2)	0.084	12 (42.9)	14 (46.7)	0.771	28 (43.1)	38 (55.9)	0.140
Week 32	18 (48.6)	24 (63.2)	0.206	11 (39.3)	14 (46.7)	0.571	29 (44.6)	38 (55.9)	0.194
Week 36	15 (40.5)	23 (60.5)	0.083	12 (42.9)	14 (46.7)	0.771	27 (41.5)	37 (54.4)	0.137
Week 40	14 (37.8)	23 (60.5)	0.049*	10 (35.7)	12 (40.0)	0.737	24 (36.9)	35 (51.5)	0.091
Week 44	12 (32.4)	22 (57.9)	0.027*	9 (32.1)	14 (46.7)	0.259	21 (32.3)	36 (52.9)	0.016*
Week 48	10 (27.0)	24 (63.2)	0.002**	8 (28.6)	14 (46.7)	0.156	18 (27.7)	38 (55.9)	<0.001***

BSA = body surface area

a. The p-value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's Exact test was used.

b. Statistically significant, ***p ≤ 0.001, **p ≤ 0.01, and *p ≤ 0.05.

Cross Reference: OLE Section 14, Table 14.2__9.

PEDACR70	MTX	
	Placebo N=37	Adalimumab N=38
Reviewer's Week 48	10 (27.0)	23 (60.5)

Table 48. PedACR90 Responders up to Week 48 (ITT Population, Double-blind Phase)

	MTX			non-MTX			Overall		
	Placebo N=37	Adalimumab 24 mg/m^2 BSA eow N=38		Placebo N=28	Adalimumab 24 mg/m^2 BSA eow N=30		Placebo N=65	Adalimumab 24 mg/m^2 BSA eow N=68	
Visit	n (%)		p-value[a,b]	n (%)		p-value[a,b]	n (%)		p-value[a,b]
Week 16	10 (27.0)	13 (34.2)	0.500	10 (35.7)	12 (40.0)	0.737	20 (30.8)	25 (36.8)	0.465
Week 20	9 (24.3)	13 (34.2)	0.347	7 (25.0)	10 (33.3)	0.486	16 (24.6)	23 (33.8)	0.244
Week 24	12 (32.4)	12 (31.6)	0.937	9 (32.1)	9 (30.0)	0.860	21 (32.3)	21 (30.90	0.860
Week 28	10 (27.0)	13 (34.2)	0.500	8 (28.6)	9 (30.0)	0.905	18 (27.7)	22 (32.4)	0.558
Week 32	11 (29.7)	15 (39.5)	0.375	5 (17.9)	9 (30.0)	0.280	16 (24.6)	24 (35.3)	0.179
Week 36	10 (27.0)	13 (34.2)	0.500	6 (21.4)	10 (33.3)	0.311	16 (24.6)	23 (33.8)	0.244
Week 40	10 (27.0)	13 (34.2)	0.500	5 (17.9)	10 (33.3)	0.179	15 (23.1)	23 (33.8)	0.170
Week 44	10 (27.0)	15 (39.5)	0.253	5 (17.9)	8 (26.7)	0.421	15 (23.1)	23 (33.8)	0.170
Week 48	10 (27.0)	16 (42.1)	0.170	5 (17.9)	9 (30.0)	0.280	15 (23.1)	25 (36.8)	0.085

BSA = body surface area

a. The p-value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's Exact test was used.

b. Statistically significant, ***p ≤ 0.001, **p ≤ 0.01, and *p ≤ 0.05.

Cross Reference: DE038 Section 14, Table 142__10.

PEDACR90	MTX	
	Placebo N=37	Adalimumab N=38
Reviewer's Week 48	9 (24.3)	17 (44.7)

Appendix 2

Table 53. PedACR30 Responders up to Week 136 (ITT Population, Open-label Extension Body Surface Area Phase)

	MTX			non-MTX			Overall		
	Adalimumab (Placebo during DB phase) N = 36	Adalimumab 24 mg/m^2 BSA eow N = 35		Adalimumab (Placebo during DB phase) N = 28	Adalimumab 24 mg/m^2 BSA eow N = 29		Adalimumab (Placebo during DB Phase) N = 64	Adalimumab 24 mg/m^2 BSA eow N = 64	
Visit	N1/N2[a] (%)		p-value[b]	N1/N2[a] (%)		p-value[b]	N1/N2[a] (%)		p-value[b]
Baseline[c]	25/33 (75.8)	30/34 (88.2)	0.183	22/27 (81.5)	24/26 (92.3)	0.420	47/60 (78.3)	54/60 (90.0)	0.080
Week 8[d]	31/31 (100.0)	32/34 (94.1)	0.493	27/27 (100.0)	25/26 (96.2)	0.491	58/58 (100.0)	57/60 (95.0)	0.244
Week 16	31/31 (100.0)	33/34 (97.1)	1.000	27/27 (100.0)	24/25 (96.0)	0.481	58/58 (100.0)	57/59 (96.6)	0.496
Week 24	29/30 (96.7)	34/34 (100.0)	0.469	26/27 (96.3)	25/26 (96.2)	1.000	55/57 (96.5)	59/60 (98.3)	0.612
Week 32	28/30 (93.3)	34/34 (100.0)	0.216	24/25 (96.0)	24/24 (100.0)	1.000	52/55 (94.5)	58/58 (100.0)	0.112
Week 40	27/27 (100.0)	34/35 (97.1)	1.000	22/23 (95.7)	23/23 (100.0)	1.000	49/50 (98.0)	57/58 (98.3)	1.000
Week 56	20/24 (83.3)	30/31(96.8)	0.156	20/21 (95.2)	20/20 (100.0)	1.000	40/45 (88.9)	50/51 (98.0)	0.095
Week 72	20/23 (87.0)	26/27 (96.3)	0.322	17/19 (89.5)	13/13 (100.0)	0.502	37/42 (88.1)	39/40 (97.5)	0.202
Week 88	15/16 (93.8)	15/16 (93.8)	1.000	12/13 (100.00)	8/9 (88.9)	0.429	27/28 (96.4)	23/25 (92.0)	0.597
Week 104	7/8 (87.5)	11/11 (100.0)	0.421	10/10 (100.0)	6/7 (85.7)	0.412	17/18 (94.4)	17/18 (94.4)	1.000
Week 120	4/5 (80.0)	6/6 (100.0)	0.455	3/3 (100.00)	2/3 (66.7)	1.000	7/8 (87.5)	8/9 (88.9)	1.000
Week 136	1/1 (100.0)	1/1 (100.0)	-	1/1 (100.0)	1/2 (50.0)	1.000	2/3 (100.00)	2/3 (66.7)	1.000

BSA = body surface area; DB = double-blind

a. N1 = number of responders, N2 = number of subjects with non-missing responses

b. The p-value based on Pearson's Chi-square test. If cell count was <5, then Fisher's Exact test was used. Statistically significant, ***$p \leq 0.001$, **$p \leq 0.01$, and *$p \leq 0.05$.

c. Response is calculated using OL LI phase Baseline.

d. Weeks 8 to 136 are calculated from the time of the first OLE BSA injection, the Baseline for the OLE BSA phase is the last non-missing value prior to first injection in OLE BSA.

Cross Reference: OLE Section 14, Table 14.2__1.1.1.1 and 14.2__1.1.1.2.

Table 54. PedACR50 Responders up to Week 136 (ITT Population, Open-label Extension Body Surface Area Phase)

	MTX			non-MTX			Overall		
	Adalimumab (Placebo during DB phase N = 36	Adalimumab 24 mg/m^2 BSA eow N = 35		Adalimumab (Placebo during DB phase) N = 29	Adalimumab 24 mg/m^2 BSA eow N = 28		Adalimumab (Placebo during DB Phase) N = 64	Adalimumab 24 mg/m^2 BSA eow N = 64	
Visit	N1/N2[c] (%)		p-value[a,b]	N1/N2[c] (%)		p-value[a,b]	N1/N2[c] (%)		p-value[a,b]
Baseline[d]	20/33 (60.6)	27/34 (79.4)	0.093	19/27 (70.4)	22/26 (84.6)	0.215	39/60 (65.0)	49/60 (81.7)	0.039
Week 8[e]	27/31 (87.1)	32/34 (94.1)	0.413	26/27 (96.3)	24/26 (92.3)	0.610	53/58 (91.4)	56/60 (93.3)	0.741
Week 16	30/31 (96.8)	31/34 (91.2)	0.615	25/27 (92.6)	23/25 (92.0)	1.000	55/58 (94.8)	54/59 (91.5)	0.717
Week 24	27/30 (90.0)	32/34 (94.1)	0.659	25/27 (92.6)	25/26 (96.2)	1.000	52/57 (91.2)	57/60 (95.0)	0.483
Week 32	27/30 (90.0)	34/34 (100.0)	0.097	23/25 (92.0)	24/24 (100.0)	0.490	50/55 (90.9)	58/58 (100.0)	0.035*
Week 40	27/27 (100.0)	33/35 (94.3)	0.500	22/23 (95.7)	23/23 (100.0)	1.000	49/50 (98.0)	56/58 (96.6)	1.000
Week 56	20 /24 (83.3)	29/31 (93.5)	0.387	20/21 (95.2)	20/20 (100.0)	1.000	40/45 (88.9)	49 /51 (96.1)	0.247
Week 72	19/23 (82.6)	25/27 (92.6)	0.395	16/19 (84.2)	13/13 (100.0)	0.253	35/42 (83.3)	38/40 (95.0)	0.156
Week 88	14/16 (87.5)	13/16 (81.3)	1.000	12/12 (100.0)	8/9 (88.9)	0.429	26/28 (92.9)	21/ 25 (84.0)	0.404
Week 104	6/8 (75.0)	10/11 (90.9)	0.546	10/10 (100.0)	6/7 (85.7)	0.412	16/18 (88.9)	16/18 (88.9)	1.000
Week 120	4/5 (80.)	6/6 (100.0)	0.455	3/3 (100.0)	2/3 (66.7)	1.000	7/8 (87.5)	8/9 (88.9)	1.000
Week 136	1/1 (100.0)	0/1 (0.0)	1.000	1/1 (100.0)	1/2 (50.0)	1.000	2/2 (100.0)	1/3 (33.3)	0.400

DB = double-blind; BSA = body surface area

a. The p-value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's Exact test was used.

b. Statistically significant, ***p ≤ 0.001, **p ≤ 0.01, and *p ≤ 0.05.

c. N1 = number of responders, N2 = number of subjects with non-missing responses

d. Response is calculated using OL LI phase Baseline.

e. Weeks 8 to 136 are calculated from the time of the first OLE BSA injection, the Baseline for the OLE BSA phase is the last non-missing value prior to first injection in OLE BSA

Cross Reference: OLE Section 14, Tables14.2__1.1.2.1 and 14.2__1.1.2.2.

Table 55. PedACR70 Responders up to Week 136 (ITT Population, Open-label Extension Body Surface Area Phase)

	MTX			non-MTX			Overall		
	Adalimumab (Placebo during DB phase N = 36	Adalimumab 24 mg/m^2 BSA eow N = 35		Adalimumab (Placebo during DB phase) N = 28	Adalimumab 24 mg/m^2 BSA eow N = 29		Adalimumab (Placebo during DB Phase) N = 64	Adalimumab 24 mg/m^2 BSA eow N = 64	
Visit	N1/N2[c] (%)		p-value[a,b]	N1/N2[c] (%)		p-value[a,b]	N1/N2[c] (%)		p-value[a,b]
Baseline[d]	12/33 (36.4)	23/24 (67.6)	0.010**	13/27 (48.1)	17/26 (65.4)	0.206	25/60 (41.7)	40/60 (66.7)	0.006**
Week 8[e]	19/31 (61.3)	26/34 (76.5)	0.185	22/27 (81.5)	20/26 (76.9)	0.682	41/58 (70.7)	46/60 (76.7)	0.461
Week 16	23/31 (74.2)	31/34 (91.2)	0.068	19/27 (70.4)	17/25 (68.0)	0.853	42/58 (72.4)	48/59 (81.4)	0.251
Week 24	23/30 (76.7)	29/34 (85.3)	0.378	20/27 (74.1)	22/26 (84.6)	0.344	43/57 (75.4)	51/60 (85.0)	0.193
Week 32	23/30 (76.7	29/34 (85.3)	0.378	19/25 (76.0)	22/24 (91.7)	0.247	42/55 (76.4)	51/58 (87.9)	0.107
Week 40	22/27 (81.5)	32/35 (91.4)	0.279	17/23 (73.9)	23/23 (100.0)	0.022*	39/50 (78.0)	55/58 (94.8)	0.009**
Week 56	18/24 (75.0)	25/31 (80.6)	0.615	16/21 (76.2)	19/20 (95.0)	0.184	34/45 (75.6)	44/51 (86.3)	0.179
Week 72	16/23 (69.6)	23/27 (85.2)	0.184	16/19 (84.2)	13/13 (100.0)	0.253	32/42 (76.2)	36/40 (90.0)	0.097
Week 88	12/16 (75.0)	13/16 (81.3)	1.000	12/12 (100.0)	8/9 (88.9)	0.429	24/28 (85.7)	21/25 (84.0)	1.000
Week 104	4/8 (50.0)	10/11 (90.9)	0.111	9/10 (90.0)	5/7 (71.4)	0.537	13/18 (72.2)	15/18 (83.3)	0.691
Week 120	4/5(80.0)	5/6 (83.3)	1.000	3/3 (100.0)	2/3 (66.7)	1.000	7/8 (87.5)	7/9 (77.8)	1.000
Week 136	1/1 (100.0)	0/1 (0.0)	1.000	0/1 (0.0)	1/2 (50.0)	1.000	1/2 (50.0)	1/3 (33.3)	1.000

DB = double-blind; BSA = body surface area

a. The p-value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's Exact test was used.

b. Statistically significant, ***$p \leq 0.001$, **$p \leq 0.01$, and *$p \leq 0.05$.

c. N1 = number of responders, N2 = number of subjects with non-missing responses

d. Response is calculated using OL LI phase Baseline

e. Weeks 8 to 136 are calculated from the time of the first OLE BSA injection, the Baseline for the OLE BSA phase is the last non-missing value prior to first injection in OLE BSA

Cross Reference: OLE Section 14, Tables 14.2__1.1.3.1 and 14.2__1.1.3.2.

Table 56. PedACR90 Responders up to Week 136 (ITT Population, Open-label Extension Body Surface Area Phase)

	MTX			non-MTX			Overall		
	Adalimumab (Placebo during DB phase) N = 36	Adalimumab 24 mg/m^2 BSA eow N = 35		Adalimumab (Placebo during DB phase) N = 28	Adalimumab 24 mg/m^2 BSA eow N = 29		Adalimumab (Placebo during DB Phase) N = 64	Adalimumab 24 mg/m^2 BSA eow N = 64	
Visit	N1/N2[c] (%)		p-value[a,b]	N1/N2[c] (%)		p-value[a,b]	N1/N2[c] (%)		p-value[a,b]
Baseline[d]	7/33 (21.2)	19/34 (55.9)	0.004**	6/27 (22.2)	9/26 (34.6)	0.317	13/60 (21.7)	28/60 (46.7)	0.004**
Week 8[e]	13/31 (41.9)	16/34 (47.1)	0.678	11/27 (40.7)	10/26 (38.5)	0865	24/58 (41.4)	26/60 (43.3)	0.830
Week 16	16/31 (51.6)	22/34 (64.7)	0.285	14/27 (51.9)	13/25 (52.0)	0.991	30/58 (51.7)	35/59 (59.3)	0.408
Week 24	17/30 (56.7)	23/34 (67.6)	0.365	13/27 (48.1)	13/26 (50.0)	0.893	30/57 (52.6)	36/60 (60.0)	0.422
Week 32	14/30 (46.7)	22/34 (64.7)	0.147	12/25 (48.0)	18/24 (75.0)	0.052	26/55 (47.3)	40/58 (69.0)	0.019*
Week 40	17/27 (63.0)	23/35 (65.7)	0.822	12/23 (52.2)	16/23 (69.6)	0.237	29/50 (58.0)	39/58 (67.2)	0.321
Week 56	14/24 (58.3)	21/31 (67.7)	0.472	12/21 (57.1)	11/20 (55.0)	0.890	26/45 (57.8)	32/51 (62.7)	0.619
Week 72	9/23 (39.1)	20/27 (74.1)	0.013*	10/19 (52.6)	8/13 (61.5)	0.618	19/42 (45.2)	28/40 (70.0)	0.023*
Week 88	7/16 (43.8)	12/16 (75.0)	0.072	7/12 (58.3)	6/9 (66.7)	1.000	14/28 (50.0)	18/25 (72.0)	0.102
Week 104	4/8 (50.0)	7/11 (63.6)	0.658	5/10 (50.0)	3/7 (42.9)	1.000	9/18 (50.0)	10/18 (55.6)	0.738
Week 120	3/5 (60.0)	4/6 (66.7)	1.000	2/3 (66.7)	2/3 (66.7)	1.000	5/8 (62.5)	6/9 (66.7)	1.000
Week 136	1/1 (100.0)	0/1 (0.0)	1.000	0/1 (0.0)	0/2 (0.0)	-	1/2 (50.0)	0/3 (0.0)	0.400

DB = double-blind; BSA = body surface area

a. The p-value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's Exact test was used.

b. Statistically significant. ***p ≤ 0.001, **p ≤ 0.01, and *p ≤ 0.05.

c. N1 = number of responders, N2 = number of subjects with non-missing responses

d. Response is calculated using OL LI phase Baseline.

e. Weeks 8 to 136 are calculated from the time of the first OLE BSA injection, the Baseline for the OLE BSA phase is the last non-missing value prior to first injection in OLE BSA

Cross Reference: OLE Section 14, Table 14.2__1.1.4.1 and 14.2__1.1.4.2.

Appendix 3

Table 3. PedACR30 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

	MTX				non-MTX				Overall			
	Adalimumab (Placebo during DB phase) N = 36		Adalimumab N = 35		Adalimumab (Placebo during DB phase) N = 28		Adalimumab N = 29		Adalimumab (Placebo during DB phase) N = 64		Adalimumab N = 64	
Visit[a]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]
OLB BSA Baseline	25/36 (69.4)	3	30/35 (85.7)	1	22/28 (78.6)	1	24/29 (82.8)	3	47/64 (73.4)	4	54/64 (84.4)	4
Week 8	32/36 (88.9)	5	32/35 (91.4)	1	27/28 (96.4)	1	25/29 (86.2)	3	59/64 (92.2)	6	57/64 (89.1)	4
Week 16	33/36 (91.7)	5	33/35 (94.3)	1	27/28 (96.4)	1	25/29 (86.2)	4	60/64 (93.8)	6	58/64 (90.6)	5
Week 24	31/35 (88.6)	5	34/35 (97.1)	1	26/28 (92.9)	1	25/29 (86.2)	3	57/63 (90.5)	6	59/64 (92.2)	4
Week 32	29/34 (85.3)	4	34/35 (97.1)	1	26/28 (92.9)	3	25/29 (86.2)	5	55/62 (88.7)	7	59/64 (92.2)	6
Week 40	29/33 (87.9)	6	34/35 (97.1)	0	25/27 (92.6)	4	24/28 (857)	5	54/60 (90.0)	10	58/63 (92.1)	5
Week 56	23/30 (76.7)	6	31/32 (96.9)	1	21/24 (87.5)	3	24/27 (88.9)	7	44/54 (81.5)	9	55/59 (93.2)	8
Week 72	22/28 (78.6)	5	30/31 (96.8)	4	19/22 (86.4)	3	21/24 (87.5)	11	41/50 (82.0)	8	51/55 (92.7)	15
Week 88	20/25 (80.0)	9	23/25 (92.0)	9	16/18 (88.9)	6	14/16 (87.5)	7	36/43 (83.7)	15	37/41 (90.2)	16
Week 104	13/15 (86.7)	7	15/15 (100.0)	4	11/12 (91.7)	2	7/9 (77.8)	2	24/27 (88.9)	9	22/24 (91.7)	6
Week 120	7/9 (77.8)	4	10/10 (100.0)	4	7/7 (100.0)	4	4/6 (66.7)	3	14/16 (87.5)	8	14/16 (87.5)	7
Week 136	5/6 (83.3)	5	6/6 (100.0)	5	1/1 (100.0)	0	1/2 (50.0)	0	6/7 (85.7)	5	7/8 (87.5)	5

a. Response was calculated using the Open-label lead-in phase baseline. DB phase values were not used to impute missing BSA phase values

b. N1 = number of responders, N2 = number of subjects present in the study at that visit

c. N3 = number of subjects with missing values, but present in study phase.

Cross reference: Tables 9__1.1 and 9__1.2

Table 4. PedACR50 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

	MTX				non-MTX				Overall			
	Adalimumab (Placebo during DB phase) N = 36		Adalimumab N = 35		Adalimumab (Placebo during DB phase) N = 28		Adalimumab N = 29		Adalimumab (Placebo during DB phase) N = 64		Adalimumab N = 64	
Visit[a]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]
OLE BSA Baseline	20/36 (55.6)	3	27/35 (77.1)	1	19/28 (67.9)	1	22/29 (75.9)	3	39/69 (60.9)	4	49/64 (76.6)	4
Week 8	28/36 (77.8)	5	32/35 (91.4)	1	26/28 (92.9)	1	24/29 (82.8)	3	54/64 (84.4)	6	56/64 (87.5)	4
Week 16	32/36 (88.9)	5	31/35 (88.6)	1	25/28 (89.3)	1	24/29 (82.8)	4	57/64 (89.1)	6	55/64 (85.9)	5
Week 24	29/35 (82.9)	5	32/35 (91.4)	1	25/28 (89.3)	1	25/29 (86.2)	3	54/63 (85.7)	6	57/64 (89.1)	4
Week 32	28/34 (82.4)	4	34/35 (97.1)	1	25/28 (89.3)	3	25/29 (86.2)	5	53/62 (85.5)	7	59/64 (92.2)	6
Week 40	29/33 (87.9)	6	33/35 (94.3)	0	25/27 (92.6)	4	24/28 (85.7)	5	54/60 (90.0)	10	57/63 (90.5)	5
Week 56	23/30 (76.7)	6	30/32 (93.8)	1	21/24 (87.5)	3	24/27 (88.9)	7	44/54 (81.5)	9	54/59 (91.5)	8
Week 72	21/28 (75.0)	5	29/31 (93.5)	4	18/22 (81.8)	3	21/24 (87.5)	11	39/50 (78.0)	8	50/55 (90.9)	15
Week 88	19/25 (76.0)	9	21/25 (84.0)	9	15/18 (83.3)	6	14/16 (87.5)	7	34/43 (79.1)	15	35/41 (85.4)	16
Week 104	12/15 (80.0)	7	13/15 (86.7)	4	11/12 (91.7)	2	7/9 (77.8)	2	23/27 (85.2)	9	20/24 (83.3)	6
Week 120	6/9 (66.7)	4	10/10 (100.0)	4	7/7 (100.0)	4	4/6 (66.7)	3	13/16 (81.3)	8	14/16 (87.5)	7
Week 136	5/6 (83.3)	5	5/6 (83.3)	5	1/1 (100.0)	0	1/2 (50.0)	0	6/7 (85.7)	5	6/8 (75.0)	5

a. Response was calculated using the Open-label lead-in phase baseline. DB phase values were not used to impute missing BSA phase values.

b. N1 = number of responders, N2 = number of subjects present in the study at that visit.

c. N3 = number of subjects with missing values, but present in study phase.

Cross reference: Tables 9__2.1 and 9__2.2

Table 5. PedACR70 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

	MTX				non-MTX				Overall			
	Adalimumab (Placebo during DB phase) N = 36		Adalimumab N = 35		Adalimumab (Placebo during DB phase) N = 28		Adalimumab N = 29		Adalimumab (Placebo during DB phase) N = 64		Adalimumab N = 64	
Visit[a]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]
OLE BSA Baseline	12/36 (33.3)	3	23/35 (65.7)	1	13/28 (46.4)	1	17/29 (58.6)	3	25/64 (39.1)	4	40/64 (62.5)	4
Week 8	20/36 (55.6)	5	26/35 (74.3)	1	22/28 (78.6)	1	20/29 (69.0)	3	42/64 (65.6)	6	46/64 (71.9)	4
Week 16	23/36 (63.9)	5	31/35 (88.6)	1	19/28 (67.9)	1	18/29 (62.1)	4	42/64 (65.6)	6	49/64 (76.6)	5
Week 24	24/35 (68.6)	5	29/35 (82.9)	1	20/28 (71.4)	1	22/29 (75.9)	3	44/63 (69.8)	6	51/64 (79.7)	4
Week 32	23/34 (67.6)	4	29/35 (82.9)	1	21/28 (75.0)	3	22/29 (75.9)	5	44/62 (71.0)	7	51/64 (79.7)	6
Week 40	23/33 (69.7)	6	32/35 (91.4)	0	20/27 (74.1)	4	23/28 (82.1)	5	43/60 (71.7)	10	55/63 (87.3)	5
Week 56	20/30 (66.7)	6	26/32 (81.3)	1	17/24 (70.8)	3	23/27 (85.2)	7	37/54 (68.5)	9	49/59 (83.1)	8
Week 72	17/28 (60.7)	5	27/31 (87.1)	4	18/22 (81.8)	3	21/24 (87.5)	11	35/50 (70.0)	8	48/55 (87.3)	15
Week 88	16/25 (64.0)	9	20/25 (80.0)	9	15/18 (83.3)	6	14/16 (87.5)	7	31/43 (72.1)	15	34/41 (82.9)	16
Week 104	7/15 (46.7)	7	13/15 (86.7)	4	10/12 (83.3)	2	6/9 (66.7)	2	17/27 (63.0)	9	19/24 (79.2)	6
Week 120	5/9 (55.6)	4	9/10 (90.0)	4	7/7 (100.0)	4	4/6 (66.7)	3	12/16 (75.0)	8	13/16 (81.3)	7
Week 136	4/6 (66.7)	5	4/6 (66.7)	5	0/1 (0.0)	0	1/2 (50.0)	0	4/7 (57.1)	5	5/8 (62.5)	5

a. Response was calculated using the Open-label lead-in phase baseline. DB phase values were not used to impute missing BSA phase values.

b. N1 = number of responders, N2 = number of subjects present in the study at that visit

c. N3 = number of subjects with missing values, but present in study phase.

Cross reference: Tables 9__3.1 and 9__3.2

Table 6. PedACR90 Responders Using the Last Observation Carried Forward for Missing Visit Value (Open-label Extension Body Surface Area Population, Open-label Extension Body Surface Area Phase)

	MTX				non-MTX				Overall			
	Adalimumab (Placebo during DB phase) N = 36		Adalimumab N = 35		Adalimumab (Placebo during DB phase) N = 28		Adalimumab N = 29		Adalimumab (Placebo during DB phase) N = 64		Adalimumab N = 64	
Visit[a]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]	N1/N2[b] (%)	N3[c]
OLE BSA Baseline	7/36 (19.4)	3	19/35 (54.3)	1	6/28 (21.4)	1	9/29 (31.0)	3	13/64 (20.3)	4	28/64 (43.8)	4
Week 8	13/36 (36.1)	5	16/35 (45.7)	1	11/28 (39.3)	1	10/29 (34.5)	3	24/64 (37.5)	6	26/64 (40.6)	4
Week 16	16/36 (44.4)	5	22/35 (62.9)	1	14/28 (50.0)	1	13/29 (44.8)	4	30/64 (46.9)	6	35/64 (54.7)	5
Week 24	18/35 (51.4)	5	23/35 (65.7)	1	13/28 (46.4)	1	13/29 (44.8)	3	31/63 (49.2)	6	36/64 (56.3)	4
Week 32	14/34 (41.2)	4	22/35 (62.9)	1	13/28 (46.4)	3	18/29 (62.1)	5	27/62 (43.5)	7	40/64 (62.5)	6
Week 40	17/33 (51.5)	6	23/35 (65.7)	0	14/27 (51.9)	4	16/28 (57.1)	5	31/60 (51.7)	10	39/63 (61.9)	5
Week 56	16/30 (53.3)	6	21/32 (65.6)	1	13/24 (54.2)	3	14/27 (51.9)	7	29/54 (53.7)	9	35/59 (59.3)	8
Week 72	10/28 (35.7)	5	22/31 (71.0)	4	12/22 (54.5)	3	13/24 (54.2)	11	22/50 (44.0)	8	35/55 (63.6)	15
Week 88	10/25 (40.0)	9	18/25 (72.0)	9	9/18 (50.0)	6	9/16 (56.3)	7	19/43 (44.2)	15	27/41 (65.9)	16
Week 104	5/13 (33.3)	7	10/15 (66.7)	4	6/12 (50.0)	2	4/9 (44.4)	2	11/27 (40.7)	9	14/24 (58.3)	6
Week 120	4/9 (44.4)	4	7/10 (70.0)	4	3/7 (42.9)	4	3/6 (50.0)	3	7/16 (43.8)	8	10/16 (62.5)	7
Week 136	4/6 (66.7)	5	4/6 (66.7)	5	0/1 (0.0)	0	0/2 (0.0)	0	4/7 (57.1)	5	4/8 (50.0)	5

a. Response was calculated using the Open-label lead-in phase baseline. DB phase values were not used to impute missing BSA phase values

b. N1 = number of responders, N2 = number of subjects present in the study at that visit.

c. N3 = number of subjects with missing values, but present in study phase.

Cross reference: Tables 9__4.1 and 9__4.2

Signature Page:

Biometrics Division

12/13/07

Joan Buenconsejo, Ph.D. Date
Statistical Reviewer

12/13/07

Dionne Price, Ph.D. Date
Biometrics Team Leader