2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Adalimumab	**Volume:**	
Name of Active Ingredient: Adalimumab	**Page:**	

Title of Study:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Efficacy, and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Children with Polyarticular Juvenile Rheumatoid Arthritis

Coordinating Investigator:

[redacted] MD, MPH, [redacted]

redacted information 24Sep2014

Study Sites:

Thirty one (31) sites in the United States and European Union.

Publications:

1 manuscript and 1 oral presentation.

Studied Period (Years): First Subject First Visit: 19 Sep 2002 Last Subject Last Visit: 02 Jun 2010	**Phase of Development:** 3

Objectives: The primary efficacy objective was to determine and compare disease flare in non-methotrexate (MTX)/adalimumab-treated polyarticular juvenile idiopathic arthritis (JIA) subjects to non-MTX/placebo-treated polyarticular JIA subjects who had previously responded to adalimumab treatment.

The primary safety objectives were: 1) To contrast the safety profile of adalimumab with placebo in non-MTX-treated subjects with polyarticular JIA; 2) To contrast the safety profile of adalimumab with placebo in concomitant MTX-treated subjects with polyarticular JIA; 3) To evaluate the long-term safety profile of repeated subcutaneous (SC) administration of adalimumab in pediatric subjects with JIA. The pharmacokinetic (PK) objective was to estimate adalimumab population pharmacokinetic parameters in pediatric subjects (at least 4 years old) with polyarticular JIA.

Objectives (Continued):

The secondary efficacy objectives were: 1) To determine and compare time to onset of flare in non-MTX/adalimumab-treated polyarticular JIA subjects to non-MTX/placebo-treated polyarticular JIA subjects; 2) To determine and compare disease flare and time to onset of flare in MTX/adalimumab-treated polyarticular JIA subjects to MTX/placebo-treated polyarticular JIA subjects; 3) To determine continued clinical benefit at the 30%, 50%, 70%, and 90% improvement response in the Pediatric American College of Rheumatology (PedACR) scores after repeated SC administration of adalimumab; 4) To compare the efficacy of fixed dose (FD) adalimumab every other week (eow) based on body weight to variable eow dosing based on body surface area (BSA) of subjects rolled-over into the Open-Label Extension (OLE) FD phase of the trial.

The secondary pharmacokinetic objectives were: 1) To characterize adalimumab PK and identify important subject characteristics that will explain PK variability in pediatric subjects with polyarticular JIA; 2) To compare adalimumab PK in children with JIA to adult rheumatoid arthritis (RA) subjects; 3) To compare the PK of fixed eow dosing based on body weight to variable eow dosing based on BSA of subjects rolled-over into the OLE FD phase of the trial whose PK samples were drawn.

This study report focuses on the efficacy and safety assessments performed in this study. [redacted] redacted information 24Sep2014

Methodology:

Study DE038 was a multicenter, Phase 3, randomized withdrawal, double-blind (DB), stratified, parallel-group study in children (4 to 17 years old) with polyarticular JIA that were either treated or not treated with methotrexate (MTX). The study consisted of 4 phases: a 16-week Open-Label Lead-In (OL LI), a 32-week DB phase, an at least 44-week OLE BSA phase, and an up to 240-week OLE FD phase. Based on the duration of the phases, the total study duration could have been up to 408 weeks (102 months). The dosing by BSA was 24 mg of adalimumab per square meter (m^2) up to a maximum of 40 mg total body dose administered SC eow. The dosing by FD in subjects weighing less than 30 kg was 20 mg of adalimumab SC eow and 40 mg SC eow in subjects weighing 30 kg or more.

Non-MTX-treated subjects who were eligible for study enrollment could have been either naïve to MTX or had been withdrawn from MTX at least 2 weeks prior to study drug administration. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to Screening.

OL LI Phase: Subjects who met all entry criteria were enrolled into one of the 2 strata (with or without concomitant MTX).

Methodology (Continued):

DB Phase: At the Week 16 visit, subjects were assessed for response, defined by the PedACR30 response criteria, i.e., an improvement of 30% or more in at least 3 of the 6 indicators of disease activity evaluated (Parent's global assessment [PGA] of subject's overall well-being by visual analog scale [VAS], Physician's global assessment [PhGA] of subject's disease severity by VAS, number of active joints [joints with swelling not due to deformity or joints with limitation of passive motion (LOM)], pain, tenderness, or both, number of joints with LOM, Childhood Health Assessment Questionnaire [CHAQ], and CRP levels), with no more than 1 indicator worsening by more than 30%. Subjects who did not respond to the OL therapy were discontinued from the study. Subjects who responded positively to the OL therapy, as determined by PedACR30 response, entered the DB period and were randomized in a 1:1 ratio to receive either adalimumab (24 mg/m^2 BSA up to a maximum of 40 mg total body dose) or placebo SC eow for an additional 32 weeks or until flare of disease, whichever was earlier. A flare was defined as a worsening of 30% or more in 3 of the 6 response variables, a minimum of 2 active joints, and no more than 1 indicator improving by 30% or more. Global assessments had to change by at least 30% on a scale of 0 to 100, when used to define flare. Subjects who experienced disease flare during the DB period or subjects who completed the DB period were given the option to enter the OLE period.

OLE BSA Phase: Subjects received OL adalimumab (24 mg/m^2 BSA up to a maximum of 40 mg total body dose SC eow) for a minimum of an additional 44 weeks. All subjects who completed the additional 44 weeks of OLE BSA treatment were given the opportunity to continue into the OLE FD period.

OLE FD Phase: This phase was implemented to gather safety and efficacy data on a fixed dosing regimen based on body weight in support of marketing approval. The rationale for supporting the indication with a FD regimen was to provide a safer and more easily managed dosing regimen and product presentation (20 mg and 40 mg pre-filled syringe) compared to the single use 40 mg vial with BSA dosing that requires measuring of appropriate volume for the required dose of study drug. In the OLE FD phase, subjects weighing less than 30 kg were dosed with 20 mg of adalimumab SC eow. Subjects weighing 30 kg or more were dosed with 40 mg of adalimumab SC eow. Subjects were able to continue in the OLE FD period for up to 240 weeks or up to 60 days following marketing approval in their respective country. EU subjects who were under 13 years of age at the time of the OLE FD Week 176 visit may have continued on adalimumab for up to an additional 68 weeks, up to OLE FD Week 240. Any of the subjects who had a 13^{th} birthday before the OLE FD Week 240 visit were to be brought in for an early termination visit as soon as possible following the 13^{th} birthday. Only when all subjects reached an age of at least 13 years and had a final evaluation, was the study completed.

Pain medications were allowed except during the 12 hours before a joint assessment.

Physical examinations, measures of disease activity, and laboratory tests were to be performed at Screening and repeated at each subsequent study visit (before the administration of adalimumab). Additionally, 30 days after the last dose of study drug was administered, a follow-up visit was to occur for all subjects. Serum was to be obtained for testing of anti-double-stranded DNA (ds-DNA) antibodies at Screening, Week 16, Week 48, and, if applicable, at the early termination visit.

Methodology (Continued):

Drug concentration data were obtained to characterize adalimumab pharmacokinetics in pediatric polyarticular JIA subjects during the OL LI, the DB, and the OLE FD phases; in the latter phase samples were collected only in subjects who changed their dose due to the switch to the FD regimen.

In the previous reports, the presentation of data captured the results from OL LI and DB phase (R&D/05/248), OL LI, DB, OLE BSA and 16 weeks OLE FD (R& D/06/604) and OL LI, DB, OLE BSA and OLE FD phase data covered up to 176 weeks (R&D/10/100). In the present report, final data from all phases of the study are presented, including up to 224 weeks of OLE FD data.

Number of Subjects (Planned and Analyzed):

Planned: ~168 subjects were planned to enter the OL LI phase of the study resulting in a total of 116 subjects (58 per stratum, 29 per treatment group) during DB phase. Sample size calculation was not applicable to the OLE BSA and OLE FD phases; however, it was anticipated that ~114 subjects would enter the OLE FD phase.

Analyzed: A total of 171 subjects who entered the OL LI phase were included in the efficacy and safety analysis. From the OL LI phase, 133 subjects were randomized into the DB phase, and were included in the analysis for both efficacy and safety through Week 48. One hundred twenty-eight subjects participated in the OLE BSA phase and 106 subjects participated in the OLE FD phase; of these 106 subjects, 62 subjects completed the OLE FD phase of the study as per protocol.

Diagnosis and Main Criteria for Inclusion:

Subjects were 4 to 17 years of age, and had a diagnosis of polyarticular JIA according to the American College of Rheumatology (ACR) criteria. If the disease was systemic onset, then the subjects were to be free of any systemic JIA manifestations for at least 3 months before the time of qualification.

At the time of study Screening, subjects were to have had continuing active disease defined as ≥ 5 swollen joints and ≥ 3 joints with LOM. These joints were not mutually exclusive.

Subjects were to have been either naïve to MTX, inadequate responders to MTX, or intolerant to MTX as defined by the subject's physician. MTX administration was to have been maintained for a minimum of 3 months prior to Screening at a dose of at least 10 mg/m^2 BSA/week in all subjects with a BSA ≤ 1 m^2 and at least 10 mg/week in those with a BSA > 1 m^2.

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

Adalimumab 24 mg/m^2 BSA eow SC (up to a maximum of 40 mg total body dose). For the OLE FD phase, a 20 mg or a 40 mg dose was administered. For all phases, a vial containing 40 mg/0.8 mL adalimumab was used and the respective amount of solution which contained the required amount of adalimumab was taken from the vial.

Throughout the study, the following bulk drug product lot numbers were used: [redacted]

Duration of Treatment:

The duration of the treatment period was up to 408 weeks; 16 weeks OL LI phase, 32 weeks DB phase, up to 136 weeks OLE BSA phase, and up to 224 weeks OLE FD phase.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Throughout the study, the following placebo bulk drug product lot numbers were available for use: [redacted]

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Criteria for Evaluation

Efficacy:

During the OL LI phase subjects were assessed for response and eligibility to enter the DB phase using the PedACR30 criteria. The primary efficacy endpoint, disease flare, was assessed during the DB phase and was defined as at least a 30% worsening in three or more of the six JIA core criteria, a 30% worsening in minimum of two active joints and a 30% improvement in not more than one of the six JIA core criteria. The JIA core criteria are: PhGA of subject's disease severity by VAS, PGA of subject's overall well-being by VAS, the number of active joints (joints with swelling not due to deformity or joints with LOM and with pain, tenderness or both), the number of joints with LOM, physical function on CHAQ, and CRP.

This definition was established in consultation with pediatric rheumatologists and the FDA and was developed to minimize the magnitude of disease worsening required before patients became eligible to receive active treatment. This low threshold for worsening was important for those subjects that were randomized to receive placebo during the DB phase.

Key secondary endpoints assessed during the study were the analysis and comparison of disease flare at Week 48, which included the time to onset (from DB Baseline) of flare for subjects in the non-MTX stratum, the time to onset (from DB Baseline) of flare for subjects treated with MTX, and the proportion of subjects with disease flare for subjects treated with MTX. Subjects were also assessed for clinical benefits of adalimumab at Screening, Baseline, Weeks 2 and 4, then every 4 weeks up to Week 48, or at early termination, and throughout the OLE phases. The assessments included the proportion of subjects with PedACR30/50/70/90 responses, PhGA of subject's disease severity, PGA of subject's overall well-being, CRP levels, and the number of active joints with swelling (joints with swelling not due to deformity, or joints with LOM, and with pain, tenderness, or both), and the number of joints with LOM.

Pharmacokinetic:

Blood for pharmacokinetic and AAA concentrations were sampled during the OL LI, DB and OLE FD phases at various time points. In the OLE FD phase, only subjects who changed their dose due to the switch to the FD design had samples taken for PK and AAA.

Safety:

Adverse events (AEs) were monitored throughout the study. Standard laboratory parameters, vital signs, and physical examinations were measured at each study visit. Serum anti-dsDNA antibodies, Serum IgG, hepatitis serologies, chest x-rays, and PPD samples were taken at the study entry screen visit.

Statistical Methods

Efficacy:

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

The four analysis sets that were used for different phases in this study report are mentioned below:

- The OL LI phase includes any ITT subject that received at least one dose of adalimumab in the OL LI period of the trial (initial 16 weeks)
- The DB phase includes any ITT subject that received at least one dose of DB medication (32 week period)
- The OLE BSA phase includes any ITT subject that received at least one OLE dose of adalimumab (32 to 136 weeks)
- The OLE FD phase includes any ITT subject that received at least one dose of adalimumab at a FD of 20 mg or 40 mg (up to 240 weeks)

The primary efficacy variable was the proportion of subjects in the non-MTX stratum who experienced disease flare in the DB phase.

The analyses of the PedACR response from all four phases of the study were used to demonstrate the efficacy of adalimumab treatment. Data from the OLE BSA phase were used to demonstrate the safety and efficacy of long-term adalimumab dosing with the BSA dosing regimen, and data from the OLE FD phase were used to support the efficacy of the FD adalimumab regimen. For the OLE FD phase, this report includes data from Week 0 through Week 240 visits, if applicable.

For categorical efficacy data, Pearson's Chi-square test was used or, in instances where at least one cell had the expected value of cell count < 5, Fisher's exact test was used. Continuous efficacy variables were summarized using n (sample size), mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum for continuous variables. For continuous variables, comparisons between groups were conducted using an analysis of covariance (ANCOVA), with the OL LI Baseline as the covariate.

Additional efficacy analyses were requested by the Food and Drug Administration (FDA). The analyses were 1) the last observation carried forward (LOCF) analysis of PedACR responders during the DB phase, 2) the summary of weight-adjusted doses based on the OLE FD Baseline for subjects in the OLE FD phase, and 3) the summary of PedACR responders by weight-adjusted dose (mg/kg) based on the OLE FD Baseline, reported as percentile of subjects.

Secondary variables were analyzed over time.

Pharmacokinetic:

Adalimumab apparent clearance (CL/F) and volume of distribution (V/F) were calculated for each subject, and the correlation of pharmacokinetic parameters with covariates (like age and weight of subjects) were analyzed using mixed effect modeling techniques. [redacted]

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Safety:

The safety analyses were performed in the ITT population, as described for efficacy analyses. Adverse events were presented separately for each study phase, and summarized into strata (MTX and non-MTX) and DB phase treatment groups (placebo and adalimumab) by frequency and percentage. In the OLE BSA phase, subjects were categorized by their DB strata and treatment group. In the OLE FD phase, subjects were categorized by their dose change from the OLE BSA phase as same/decreased or increased. Subjects were further categorized by the amount of dose increases (5, 10, or > 10 mg adalimumab).

AEs that were serious, severe or life threatening, which led to premature discontinuation of the study drug, or were considered special (injection site reactions, hepatic related AEs, allergic related AEs, infectious AEs, serious infectious AEs, opportunistic infections, serious and non-serious blood dyscrasias, malignancies, non-melanoma skin cancer, CNS demyelinating diseases, lupus-like reactions, fatal AEs, and deaths), were summarized separately. Vital signs and laboratory data were described by treatment group and visit using statistical characteristics. Values outside the laboratory-specific normal range were flagged. Laboratory shift tables were also provided.

Summary/Conclusions

Key Demographic Characteristics:

The table below presents the key demographic characteristics for all ITT study phases. In the OLE FD phase, which designated groups by same/decreased adalimumab dose or increased dose compared to OLE BSA doses, statistically significant differences between treatment groups were observed in the means for age, age category, weight, and body mass index. This was not unexpected since it was more likely that older and heavier subjects were already on the 40 mg dose during the OLE BSA phase based on the subjects' BSA, and could not graduate to a higher dosage regimen, therefore generally populating the same/decreased group; whereas the younger, lighter subjects had the opportunity to increase study drug doses, and therefore generally populated the increased dose groups. The mean values for these parameters between MTX strata, however, were comparable.

Demographic Data (OL LI Phase)		
	Adalimumab 24 mg/m^2 BSA eow	
Demographic Characteristic	**MTX N = 85**	**non-MTX N = 86**
Age (years)		
Mean ± SD	11.4 ± 3.32	11.1 ± 3.75
Sex, n (%)		
Female	68 (80.0)	67 (77.9)
Male	17 (20.0)	19 (22.1)
Duration of JIA (years)		
N	84	86
Mean ± SD	4.0 ± 3.26	3.6 ± 4.04

Demographic Data (DB Phase)				
	MTX		Non-MTX	
Demographic Characteristic	**Placebo N = 37**	**Adalimumab 24 mg/m^2 BSA eow N = 38**	**Placebo N = 28**	**Adalimumab 24 mg/m^2 BSA eow N = 30**
Age (years)				
Mean ± SD	10.8 ± 3.36	11.7 ± 3.29	11.3 ± 3.77	11.1 ± 4.13
Sex, n (%)				
Female	30 (81.1)	30 (78.9)	20 (71.4)	23 (76.7)
Male	7 (18.9)	8 (21.1)	8 (28.6)	7 (23.3)
Duration of JIA (years)				
N	37	37	28	30
Mean ± SD	4.0 ± 3.54	4.3 ± 4.07	2.9 ± 3.26	3.6 ± 4.04

Key Demographic Characteristics (Continued):

Demographic Data (OLE BSA Phase)

	MTX		Non-MTX	
Demographic Characteristic	**Placebo N = 36**	**Adalimumab 24 mg/m^2 BSA eow N = 35**	**Placebo N = 28**	**Adalimumab 24 mg/m^2 BSA eow N = 29**
Age (years)				
Mean ± SD	10.9 ± 3.37	11.7 ± 3.26	11.3 ± 3.77	11.1 ± 4.21
Sex, n (%)				
Female	29 (80.6)	27 (77.1)	20 (71.4)	22 (75.9)
Male	7 (19.4)	8 (22.9)	8 (28.6)	7 (24.1)
Duration of JIA (years)				
N	36	34	28	29
Mean ± SD	4.1 ± 3.55	3.9 ± 3.60	2.9 ± 3.26	3.8 ± 4.05

Demographic Data (OLE FD Phase)

	MTX		Non-MTX	
Demographic Characteristic	**Same/Decreased N = 28**	**Increased N = 31**	**Same/Decreased N = 25**	**Increased N = 22**
Age (years)				
Mean ± SD	12.6 ± 3.33	9.8 ± 2.86	12.1 ± 4.28	9.8 ± 3.62
Sex, n (%)				
Female	20 (71.4)	25 (80.6)	17 (68.0)	16 (72.7)
Male	8 (28.6)	6 (19.4)	8 (32.0)	6 (27.3)
Duration of JIA (years)				
N	27	31	25	22
Mean ± SD	3.4 ± 3.08	4.6 ± 3.58	2.7 ± 3.38	3.5 ± 3.69

Efficacy Results:

In the DB phase, adalimumab treatment was superior to placebo in decreasing the number of disease flares in subjects in the non-MTX stratum: a statistically significantly higher proportion of subjects in the placebo treatment group demonstrated disease flare compared to subjects in the adalimumab treatment group.

	Non-MTX		
	Placebo (N = 28)	**Adalimumab (N = 30)**	
Disease Flare During the DB Phase	**n (%)**		***P* value[a]**
Disease Flare[b]	20 (71.4)	13 (43.3)	0.031

a. The *P* value is based on a Chi-square test.

b. Missing values were treated as disease flare (imputation 1).

Efficacy Results (Continued):

Secondary analyses of PedACR30/50/70/90 response at the end of the DB phase (imputing subjects with flare as non-responders) of the study demonstrated that in combined strata, subjects treated with adalimumab demonstrated statistically significant ($P = 0.048$) PedACR30 responses as early as Week 36. PedACR30 responses were achieved by 64.7% of adalimumab-treated subjects and 47.7% of placebo-treated subjects. Also, a greater proportion of placebo-treated subjects in the non-MTX stratum lost their PedACR70 response compared to adalimumab-treated subjects. Specifically at Week 48, 46.7% of adalimumab-treated subjects were PedACR70 responders vs. 60.0% at Week 16. For the placebo-treated subjects, 28.6% were PedACR70 responders at Week 48 versus 71.4% at Week 16. In the MTX stratum, adalimumab treatment was statistically superior to placebo in achieving PedACR30/50/70 responses ($P = 0.028$; $P = 0.028$, and $P = 0.002$, respectively) at Week 48.

Response using a LOCF analysis at the end of the DB phase showed that a large proportion of the subjects were PedACR30 responders irrespective of whether or not a subject met the pre-defined definition of flare. PedACR50/70/90 responses were also seen for all treatment groups. These high response rates at the time of flare are a result of the definition of flare that was developed to minimize the magnitude of worsening and to minimize the duration of inadequate treatment for subjects randomized to receive placebo during the DB phase. Despite this low threshold for flare, a significant difference in flare rates was still demonstrated when comparing the adalimumab and placebo groups in both strata.

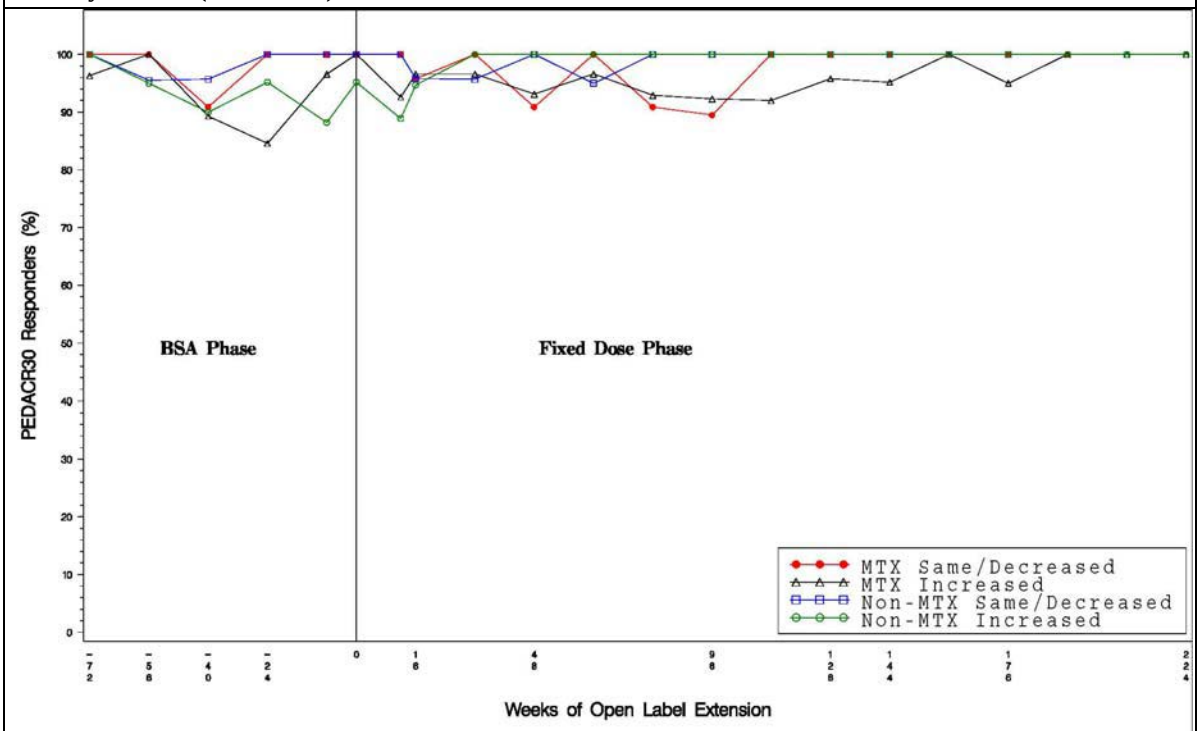
The continued benefit of adalimumab treatment was assessed during the OLE phases of the study. The figure below presents PedACR30 responses during the OLE BSA and OLE FD phases by stratification and dose change compared to DB treatment assignment. The results demonstrate that the proportion of subjects with a PedACR30 response during the OLE BSA phase was consistent (at least 84%) between MTX strata and dose change groups. Throughout the OLE FD phase, at least approximately 90% of subjects in all treatment groups were PedACR30 responders.

Sustained efficacy during the OLE BSA phase was also demonstrated for PedACR50/70/90 responses.

In the OLE FD phase, the adalimumab dose in 53 subjects was either not changed or was decreased in comparison to the dose received during the OLE BSA phase, and 53 subjects had an increase in dose. Given the small sample size for the group that decreased dose (n = 3 subjects), for purposes of analysis, these subjects were combined with the group of subjects that did not change dose during the 224 actual weeks of OLE FD treatment.

During the OLE FD phase, generally greater than 90% of subjects maintained PedACR responses regardless of whether they remained on the same dose/decreased dose or increased dose compared to the dose received during the OLE BSA period. By about Week 112, 100% of subjects in 3 of the 4 treatment groups were PedACR responders (fewer subjects in the MTX increased dose group were responders), and these treatment groups maintained these proportions of responders through study completion. Similar results were demonstrated in the OLE FD phase for measures of PedACR50/70/90.

Efficacy Results (Continued):



In addition to analyzing the response by the amount of dose change, an analysis was conducted to compare the response during the OLE FD phase depending upon the amount of adalimumab in mg/kg per body weight administration. The range of doses received varied from a minimum of 0.37 mg/kg to a maximum of 1.31 mg/kg during the OLE FD phase. This compares to a range of doses of 0.40 mg/kg to a maximum of 1.01 mg/kg received during the BSA phase.

The table below shows that, when adjusting dose according to weight, the proportion of subjects achieving a PedACR30 response during the 224 weeks of the OLE FD phase was similar in all percentile dose subgroups, including the highest and lowest mg/kg dose subgroups. Similar results are seen for PedACR50/70. The efficacy data during the 224 weeks of the OLE FD phase support the proposed FD regimen based on body weight.

Efficacy Results (Continued):						
	Min to < P5[a,b]	**P5 to < P25**	**P25 to < P50**	**P50 to < P75**	**P17 to < P95**	**P95 to Max**
	Number of PedACR30 Responders (N[c] [%])					
OLE FD Baseline	4/4 (100)	20/20 (100)	23/23 (100)	25/26 (96)	19/19 (100)	6/6 (100)
Week 12	2/2 (100)	10/10 (100)	11/12 (92)	12/12 (100)	8/9 (88.89)	1/3 (33)
Week 16	3/4 (75)	20/20 (100)	23/23 (100)	23/ 25 (92)	18/19 (95)	5/5 (100)
Week 32	3/4 (75.00)	19/19 (100.00)	23/23 (100.00)	23/23 (100.00)	17/18 (94.44)	5/5 (100.00)
Week 48	5/5 (100)	16/17 (94)	23/24 (95)	22/22 (100)	17/18 (94)	4/5 (80)
Week 96	4/4 (100)	15/15 (100)	18/20 (90)	21/21 (100)	14/15 (93)	3/4 (75)
Week 112	4/4 (100.00)	14/14 (100.00)	17/17 (100.00)	19/19 (100.00)	13/14 (92.86)	¾ (75.00)
Week 128	4/4 (100)	12/12 (100)	15/15 (100)	16/16 (100)	11/12 (91)	4/4 (100)
Week 144	4/4 (100)	9/9 (100)	11/11 (100)	12/12 (100)	9/10 (90)	3/3 (100)
Week 160	2/2 (100.00)	8/8 (100.00)	10/10 (100.00)	10/10 (100.00)	8/8 (100.00)	3/3 (100.00)
Week 176	1/1 (100)	8/8 (100)	10/10 (100)	7/8 (87)	8/8 (100)	3/3 (100)
Week 192	--	2/2 (100.00)	1/1 (100.00)	1/1 (100.00)	1/1 (100.00)	1/1 (100.00)
Week 208	1/1 (100.00)	--	1/1 (100.00)	1/1 (100.00)	1/1 (100.00)	1/1 (100.00)
Week 224	1/1 (100.00)	--	--	1/1 (100.00)	--	1/1 (100.00)
Final visit[d]	4/5 (80.00)	21/22 (95.45)	21/23 (91.30)	22/25 (88.00)	19/20 (95.00)	5/6 (83.33)

a. P = percentile.

b. Percentiles were based on the calculation of N2 subjects at that visit. Min to < P5 = 0.37 to < 0.46, P5 to < P25 = 0.46 to < 0.62, P25 to < P50 = 0.62–< 0.78, P50 to < P75 = 0.78 to < 0.95, P75 to < P95 = 0.95 to < 1.23, P95 to Max = 1.23 –< 1.31.

c. N = number of subjects with non-missing responses at each visit.

d. Final visit = the last observation of each subject in the FD population.

Pharmacokinetic Results:

Overall rate of AAA+ subjects was 15.8% (27 of 171) in the OL LI and DB phases (R&D/05/763). In those subjects that were AAA+ serum adalimumab concentrations dropped rapidly and for most subjects remained undetectable. Only 1 of 19 (5.3%) AAA+ subjects discontinued during the OL LI phase compared to 10 of 152 (6.6%) AAA- subjects. Zero of sixteen AAA+ subjects discontinued during the DB phase compared to 5 of 117 (4.3%) AAA- subjects. In the OL LI phase, a significant proportion of AAA+ subjects achieved a PedACR30 response relative to the AAA- group (86.8%). Similar results were seen in the DB phase and the OLE FD phase [redacted] No increase in AEs was seen when comparing events in the AAA+ group to the AAA- group. redacted information 24Sep2014

Safety Results:

Adalimumab was safe and well tolerated by subjects with JIA. Mean changes in vital signs were clinically unremarkable and abnormal laboratory values were not clinically relevant. No TNF-α related AEs (deaths, malignancies, lupus-like reactions, demyelinating events, non-melanoma skin cancer, or CHF) were reported in any phase of the study. In the OL LI phase, 8 subjects reported SAEs. A similar proportion of subjects in each stratum reported any AE (87.1% in the MTX stratum and 82.6% in the non-MTX stratum). There were 2 serious infectious AEs. Injection site reactions, immunologic reactions, infections, and AEs that were at least possibly related to study drug were similar between strata. The number of subjects reporting AEs leading to discontinuation of study drug was slightly increased in the non-MTX stratum compared to the MTX-stratum (8.1% versus 2.4%). This difference was not considered clinically relevant.

In the DB phase, 6 subjects reported SAEs. Five subjects reported immunologic reactions, all of whom received adalimumab treatment – 2 (5.3%) in the MTX stratum and 3 (10.0%) in the non-MTX stratum. Infections, AEs at least possibly related to study drug, and injection site reactions were all reported by similar proportions of subjects in all treatment groups, although placebo-treated subjects in the non-MTX stratum reported fewer of these AEs than other subjects.

In the combined OL LI and DB phases, AEs with the greatest incidence rate were infection and injection site reactions, (244.9 events per 100 PYs, and 512.5 events per 100 PYs, respectively). These AEs remained the most frequently reported in the OLE BSA/FD phases (114.6 events per 100 PYs and 53.6 events per 100 PYs, respectively); however, the incidence rates for these AEs were smaller in the OLE BSA/FD phase than in the OL LI/DB phase. Adverse events that were at least possibly related to study drug followed the same pattern; potential positive causality of AEs by study drug was reported less frequently in the OLE BSA/FD phase (94.5 events per 100 PYs) compared to the OL LI/DB phase (732.4 events per 100 PYs). Throughout the study and up to Week 224 of the OLE FD phase, no new safety signals were observed. No cases of tuberculosis were reported. In fact, with increased study drug exposure, incidence rates of the most frequently reported AEs decreased during the OLE BSA/FD phase compared to the OL LI/DB phase.

An overview of events of special interest across phases for subjects in the OLE FD population who took adalimumab during the DB phase are shown below:

Safety Results (Continued):		
Overview of the Treatment-Emergent Adverse Events per 100 - PYs (ITT Population, Exposure to Adalimumab) for Randomized OLE FD Population	**OL LI/ DB (N = 55) PYs = 44.1**	**OLE BSA/ OLE FD (N = 55) PYs = 244.4**
Adverse Event	**E (E/100 PYs)**	
Any AE	568 (1288.0)	846 (346.2)
At least possibly related to drug	323 (732.4)	231 (94.5)
Severe AE	3 (6.8)	21 (8.6)
Serious AE	2 (4.5)	21 (8.6)
Leading to discontinuation of study drug	0	3 (1.2)
At least possibly related to drug serious AE	0	6 (2.5)
Infections	108 (244.9)	280 (114.6)
Serious infections	2 (4.5)	5 (2.0)
Malignancies	0	0
Lymphomas	0	0
Non-melanoma skin cancer	0	0
Injection site reaction related	226 (512.5)	131 (53.6)
Opportunistic infections (excluding TB)	0	0
Congestive heart failure related	0	0
Demyelinating disease related	0	0
Hepatic-related	7 (15.9)	7 (2.9)
Allergic reactions	5 (11.3)	4 (1.6)
Lupus-like syndrome	0	0
Hematologic related	4 (9.1)	1 (0.4)
Serious blood dyscrasias	0	0
Non-serious blood dyscrasias	5 (11.3)	4 (1.6)
Fatal AEs	0	0
Death	0	0

Conclusions:

Subjects with JIA who were administered adalimumab experienced fewer disease flares than did subjects who were administered placebo. Safety data show that adalimumab was generally safe and well tolerated and shares a similar profile to other adalimumab trials in adult subjects. No trends of clinical concern were observed for any safety parameter. Safety and efficacy were demonstrated over the length of the study period (approximately 8.5 years for subjects completing the OLE FD phase). The FD regimen of 20 mg eow for subjects weighing < 30 kg and 40 mg eow for subjects weighing ≥ 30 kg is supported by the data presented for the OLE FD phase, in addition to the BSA dosing of 24 mg adalimumab/m^2 as studied in the OL LI, DB, and OLE BSA phases of the study. Hence, the overall risk-benefit ratio is favorable for adalimumab treatment of subjects with JIA.