Team Leader Memo: Addendum

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Addendum to Cross Discipline Team Leader Memorandum

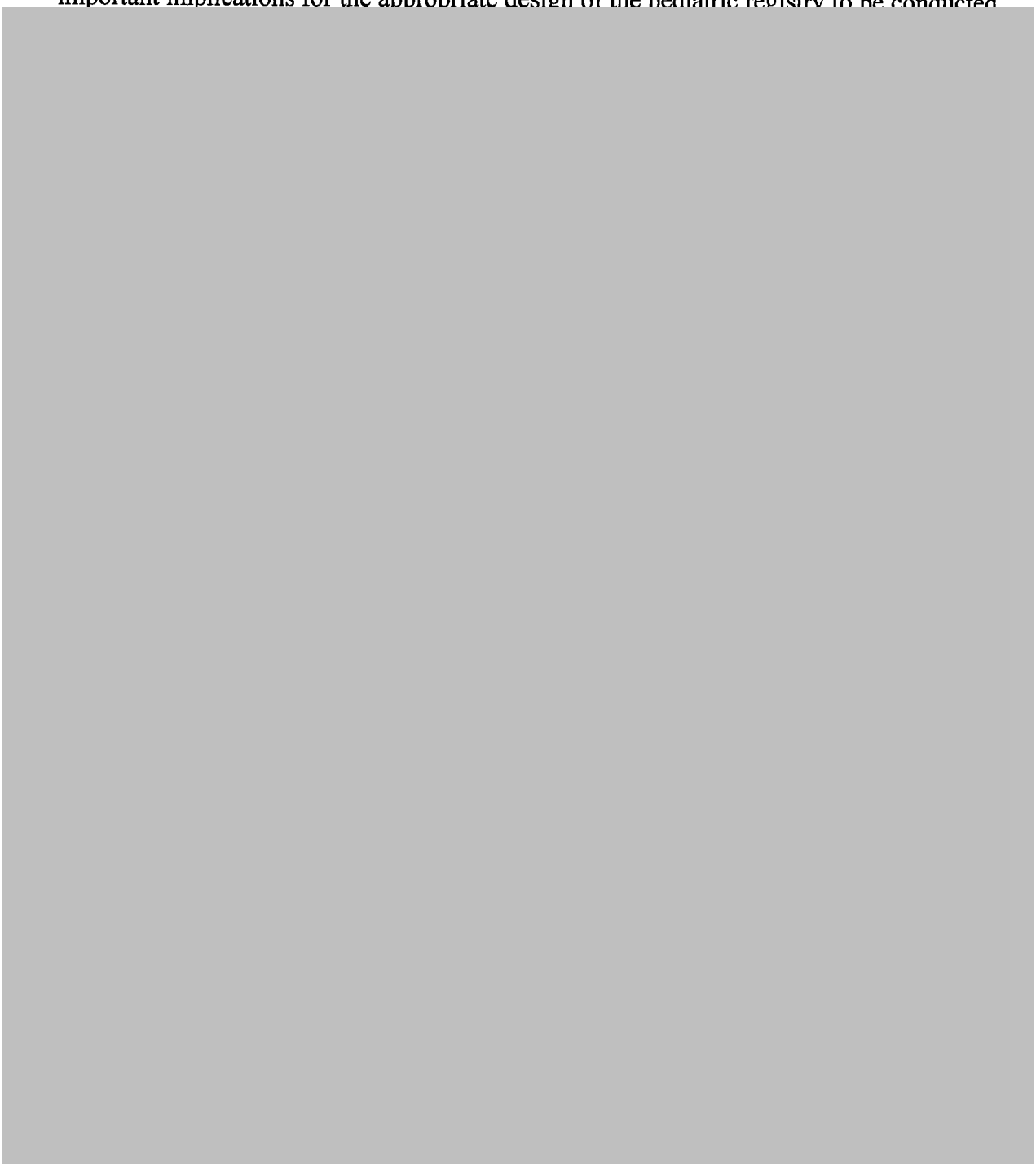
Date: February 13, 2008

To: File, BLA 125057/114

From: Jeffrey Siegel, M.D. JS 2/13/08
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: BLA supplement 125057/114
Adalimumab (Humira)
Abbott Laboratories
Proposed indication: Juvenile rheumatoid arthritis

This addendum documents new information relevant to the BLA supplement for the use of adalimumab (Humira) in children with juvenile idiopathic arthritis (JIA) with important implications for the appropriate design of the pediatric registry to be conducted



Team Leader Memo

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Cross Discipline Team Leader Memorandum

Date: January 7, 2008

To: File, BLA 125057/114

From: Jeffrey Siegel, M.D. JS 1/7/08
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: BLA supplement 125057/114
Adalimumab (Humira)
Abbott Laboratories
Proposed indication: Juvenile rheumatoid arthritis

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1. Introduction to Review

The applicant, Abbott Laboratories, is submitting this biologic licensing application supplement (s-BLA) for adalimumab (Humira) for the treatment of children with juvenile rheumatoid arthritis (JRA). Adalimumab is a recombinant human monoclonal antibody directed against tumor necrosis factor-α (TNF-α). It is approved for the treatment of adults with rheumatoid arthritis (RA) and for Crohn's disease. The applicant conducted a randomized trial in children with JRA to fulfill a post-marketing commitment (PMC). The study consisted of an initial open-label lead-in study followed by a randomized withdrawal study. After the randomized withdrawal study the children were enrolled in an open-label extension study to assess long-term safety and efficacy and a study of switching from weight-based dosing to the fixed dosing proposed for marketing. A total of 171 children with JRA were enrolled initially and 133 were subsequently entered into the randomized withdrawal portion of the study. Based on these data the applicant is proposing a dose regimen for marketing of 20 mg adalimumab subcutaneously (SQ) every other week (qow) for children weighing less than 30 kg and 40 mg of adalimumab SQ qow for children weighing 30 kg or more. Overall, the safety database consisted of 171 patients treated overall, 130 treated for 6 months or longer and 126 treated for 1 year or longer. A total of 92 children were treated for 3 years or longer.

Review of this application did not reveal major issues involving clinical efficacy or clinical pharmacology. Safety was similar to that seen in adults but there were several safety signals not observed in the adults, including elevations of creatine phosphokinase (CPK). In addition, a higher rate of immunogenicity was observed in children as compared to adults as well as a higher rate of non-serious hypersensitivity reactions. There was disagreement between the primary clinical reviewer and the secondary reviewer on the specific details of the post-marketing registry that should be conducted. This memo will review the regulatory background for this application, the evidence supporting efficacy and safety of adalimumab in children with JRA and key findings in other disciplines and carefully consider what sort of pediatric registry is warranted as a post-marketing commitment.

2. Background – Regulatory history

Based on the Pediatric Research Equity Act (PREA), when adalimumab was approved for treatment of adults with RA, the sponsor was expected to carry out pediatric assessments as well. The childhood illness most similar to RA in adults is JRA. However, JRA in children is not identical to RA in adults. Rather, JRA consists of three subtypes of disease, namely polyarticular, pauciarticular and systemic JRA. The RA guidance document recognizes the polyarticular form as the form most similar to adult RA based on similar signs and symptoms, synovitis and a similar response to existing pharmacotherapy (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX), corticosteroids). Following the approval of adalimumab for adults with RA Abbott agreed to a PMC to conduct a clinical trial to assess the efficacy and safety of adalimumab in children. The results of that trial form the basis for this efficacy supplement.

The age distribution of JRA is bimodal. There is a group of children who develop JRA at a very young age, i.e., below age 4, and another group with onset between age 4 and adolescence. It is difficult to study children younger than 4 in clinical trials because it is difficult to recruit such trials and because the outcome measures that have been validated in older children have not been validated in children younger than age 4. To fulfill the provisions of PREA, for products approved for adult RA, the Agency has generally requested sponsors conduct randomized, controlled efficacy studies in children 4 and older and to collect safety data in registries for children aged 2-4. This procedure was followed for etanercept (Enbrel), another TNF blocker. The sponsor for etanercept, Amgen/Immunex, conducted a clinical trial in children aged 4 and older that demonstrated efficacy. They obtained approval for JRA down to age 4. Subsequently, based on safety data in children aged 2-4 enrolled in a registry, the approved age range was extended down to 2 years of age.

The design of clinical trials in children with polyarticular JRA has been different from the usual design for adults with RA. In adults, clinical trials generally enroll patients with active disease and randomize them to study drug or placebo. In children with JRA it is considered unethical to treat children with active disease with a placebo given by injection. To address this concern a randomized withdrawal design is often used in situations where the study drug is already shown efficacious in adults. In this way no child receives a placebo injection unless they have experienced a clinical benefit from their study participation. In a randomized withdrawal study all enrolled children receive the study drug open label. After an appropriate time the children are assessed for their response. Responders to open-label study drug are randomized to stay on drug or withdraw to placebo. Efficacy is assessed based on an increased propensity to flare for children withdrawn to placebo. This type of design was utilized in the clinical trial of etanercept in JRA and was the basis for the subsequent approval.

The PMC to assess the effects of adalimumab in children included a commitment to conduct a clinical trial in children with JRA age 4 and older as well as a commitment to assess the feasibility of studying children under age 4. In a teleconference held in February, 2005,

Abbott has been granted orphan status for adalimumab for JRA.

3. CMC/Microbiology/Device

The product review team had no issues for this application. The application proposed a syringe with a new dose strength (20 mg/0.4 mL). The data supporting this new dose strength were adequate.

4. Nonclinical Pharmacology/Toxicology

There are no unresolved Pharmacology/Toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review of this application determined that the blood levels of adalimumab with dosing based on body surface area were similar to those seen in adults. When children were switched to fixed dosing, where children under 30 kg received 20 mg SC and children 30 kg and over received 40 mg, blood levels were also similar to those seen in adults. There were no unresolved clinical pharmacology issues.

6. Clinical/Statistical

6.1. General Discussion

The applicant undertook the clinical development program in children with polyarticular JRA in fulfillment of a PMC following the approval of adalimumab in adults with RA. The trial was a randomized withdrawal study, which is a design that has been accepted previously by the Agency to establish efficacy in children for products that have previously been demonstrated efficacious in adults with RA. The study consisted of an initial open-label lead-in study. Responders in the lead-in study were enrolled in the randomized withdrawal study. The endpoints used for the open-label, lead-in portion and the randomized withdrawal portion of the trial are standard outcome measures and were similar to those deemed acceptable by the Agency in other studies. All patients were subsequently enrolled in a long-term, open-label extension study to evaluate long-term safety and efficacy. Then patients were switched to a fixed dose regimen using the regimen proposed for marketing. The Agency has accepted a single trial in JRA for approval for products previously shown efficacious in adults based on the similarity of polyarticular JRA to adult RA.

The trial demonstrated efficacy of adalimumab in JRA and there were no issues regarding efficacy. With respect to safety, there was no placebo-controlled assessment of safety because all subjects received adalimumab owing to the randomized withdrawal design. Overall, the adverse event profile in children was similar to that seen in adults with a few exceptions. Elevations of CPK were seen in some of the children but not in adults. In addition, immunogenicity was more frequently observed in children than in adults as well as non-serious hypersensitivity reactions. Overall the risk/benefit relationship was favorable in the JRA patient population.

6.2. Efficacy

6.2.1. Dose identification/selection and limitations

The dose selected for children with JRA was based on modeling from studies in patients with RA. The dose selected in the initial portions of the trial was 24mg/m^2 adalimumab subcutaneously (SQ) qow, which produced blood levels in the same range as that seen in adults. For the fixed dose portion of the trial a dose of 40 mg SC biw was used for children weighing 30 kg or more and a dose of 20 mg SC biw for those weighing less than 30 kg. The fixed doses administered also produced blood levels similar to levels seen in adults. These data, along with the clinical trial data, are adequate to establish a safe and effective dose in this patient population.

6.2.2. Phase 3/ clinical studies essential to regulat,ory decision

The applicant submitted results of a single, double-blind, placebo-controlled, randomized withdrawal study in children with polyarticular course JRA. Study DE083 enrolled children age 4-17 with polyarticular JRA based on American College of Rheumatology (ACR) criteria. Patients needed to have at least 5 swollen joints and at least 3 joints with limitation of motion. Patients needed to have had an inadequate response to a course of NSAIDs. Patients could be either naïve to MTX, intolerant to MTX or have an inadequate response to MTX defined as the persistence of active arthritis. The study was stratified based on concomitant MTX (yes or no). Stable NSAID's and low dose corticosteroids (no more than 0.2 mg/kg/d prednisone or its equivalent) were permitted. Patients could not have received other disease-modifying anti-rheumatic agents or intra-articular corticosteroids in the period prior to enrollment. Patients with a chronic infection or an active acute infection were excluded.

Upon enrollment all patients received adalimumab open-label at a dose of 24 mg/kg SC qow to a maximum of 40 mg. After 16 weeks, patients were assessed for their response based on whether they met pedi ACR 30 criteria for response. The pedi ACR 30 is a validated response criterion, endorsed by the ACR, defined as improvement of at least 30% in 3 or more of the 6 core set criteria and worsening of no more than 30% in any one of the 6 criteria. The 6 core set criteria consist of the active joint count, the number of joints with limitation of motion, the physician's assessment of disease activity, the subject or parent assessment of disease activity, the childhood disability Health Assessment Questionnaire (DICHAQ) and acute phase reactants (C-reactive protein).

Patients achieving a pedi ACR 30 response in the open-label portion of the trial were randomized to continue on adalimumab or to receive placebo for up to 32 weeks. The primary endpoint for the randomized withdrawal phase of the trial was the proportion of patients experiencing a flare of disease in the stratum of patients not receiving concomitant MTX. A flare of disease was defined as 1) worsening of 30% or more in at least three of the six JRA core set criteria and a minimum of two active joints, and 2) improvement of 30% or more in no more than one of the six JRA core set criteria as compared to baseline values for the double-blind portion of the trial. The prespecified statistical test was a chi-square test. The primary analysis population was the ITT population. The prespecified imputation technique imputed missing data as a disease flare.

The conduct of the study was acceptable and did not raise any issues that could affect the interpretation of the data. There was little missing data. Overall, 93% of all enrolled subjects completed the open-label phase of the study and 96% of all patients randomized in the double-blind withdrawal portion completed that phase. The demographics were consistent with the general polyarticular JRA population with a mean age of 11 and good representation of younger and older age groups. As a group patients had moderately to severely active disease with a mean duration of disease of 2 years, a mean of 13 tender and 16 swollen joints and 14 joints with limitation of motion in the primary analysis population.

The majority of patients responded to adalimumab in the open-label, lead-in phase of the study. As shown in Table 1 (this and all other tables and figures copied from Dr. Larissa Lapteva's review), 94% of the patients in the MTX stratum and 74% of the patients in the arm receiving adalimumab alone responded by week 16 based on the pedi ACR 30. More than half the children who ultimately responded had a pedi ACR 30 response by week 2 with additional responses accruing in the remaining 14 weeks. Substantial numbers of patients experienced higher levels of response as well, i.e., pedi ACR 50 and 70 responses. As shown in Table 2 (modified from the clinical review of Dr. Larissa Lapteva) improvement was seen in all 6 core set variables.

Table 1: PedACR response rates in the open-label lead-in phase

	MTX + adalimumab N=85				Adalimumab N=86			
Time points	PedACR 30	PedACR 50	PedACR 70	Ped ACR 90	Ped ACR 30	Ped ACR 50	PedACR 70	Ped ACR 90
Week 2	46 (54)	24(28)	7(8)	1(1)	57 (66)	36 (42)	14(16)	1(1)
Week 4	63 (74)	41(48)	18(21)	2(2)	63 (77)	45 (52)	22(26)	3(4)
Week 8	74 (87)	64(75)	38(45)	7(8)	60 (70)	47 (55)	28(33)	6(7)
Week 12	75 (88)	71(84)	46(54)	21(25)	67 (78)	59 (69)	39(45)	10(12)
Week 16	80 (94)	77(91)	60(71)	24(28)	64 (74)	55 (64)	40(46)	22(26)

Table 2: Mean percent changes (and mean absolute changes for CRP) from baseline in JRA core variables

	Physician Global		Parent Global		N active joints	
	MTX	Non-MTX	MTX	Non-MTX	MTX	Non-MTX
Baseline (VAS, 0-100)	58	60	43	53	15	19
% change at Week 16	-71	-64	-59	-49	-71	-56
	Joints with LOM (N)		CRP (mg/dl)*		CHAQ	
Baseline	13	14	2.3	2.9	0.9	1.2
% change at Week 16	-65	-44	25 (-1.8)	-24 (-1.6)	-64	-34

At the end of the open-label, lead-in phase patients with a pedi ACR 30 response were randomized to continue adalimumab or be withdrawn to placebo. As shown in Table 3, a statistically significantly greater proportion of subjects withdrawn to placebo experienced a flare compared to patients who remained on adalimumab. Higher rates of flare upon withdrawal from adalimumab were seen both in the non-MTX stratum (the primary analysis population) and in the MTX stratum. Similar results were seen using sensitivity analyses employing different imputation techniques for missing data. Subgroup analyses

subsetting patients based on demographic characteristics or on baseline disease characteristics all showed higher rates of flare on withdrawal to placebo, indicating that the positive results with adalimumab were not restricted to any one subgroup.

Table 3: Proportion of subjects with flares in the DB phase

Stratum	Placebo	Adalimumab	p-value
Non-MTX	20/28 (71%)	13/30 (43%)	0.031
MTX	24/37 (65%)	14/38 (37%)	0.015

Clinical responses were maintained in the open-label extension phases using body surface area for dosing and fixed doses.

6.2.3. Other efficacy studies

None

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical reviewer concluded that the data provided statistically significant and consistent support for the efficacy of adalimumab in children with polyarticular JRA and that sensitivity and subgroup analyses further support the clinical benefits of adalimumab. The statistical reviewer concurred that the results supported the efficacy of adalimumab in this patient population.

6.2.5. Discussion of notable efficacy issues

There are no notable efficacy issues.

6.3. Safety

6.3.1. General safety considerations

The safety database for adalimumab in polyarticular JRA consists of the patients receiving adalimumab in the open-label, lead-in phase, the randomized withdrawal phase and the two extension phases. Overall 171 patients received at least one dose of adalimumab (Table 4). A total of 130 patients received adalimumab for 6 months or longer; 126 for 1 year or longer and 103 for 3 years or longer. This size safety database is adequate given the size of the JRA population in the US (10-20,000 patients).

Table 4: Number of subjects by duration of treatment

Duration of treatment	Number of subjects	Percent
1 - 113 DAYS	171	(100)
114 - 197 DAYS	131	(76.6)
198 - 281 DAYS	130	(76.0)
282 - 365 DAYS	128	(74.9)
366 - 449 DAYS	126	(73.7)
450 - 533 DAYS	124	(72.5)
534 - 617 DAYS	116	(67.8)
618 - 701 DAYS	115	(67.3)
702 - 785 DAYS	111	(64.9)
786 - 869 DAYS	108	(63.2)
870 - 953 DAYS	107	(62.6)
954 - 1037 DAYS	105	(61.4)
1038 - 1121 DAYS	103	(60.2)
1122 - 1205 DAYS	92	(53.8)
1206 - 1289 DAYS	73	(42.7)
1290 - 1373 DAYS	44	(25.7)
1374 - 1457 DAYS	24	(14.0)
1458 - 1541 DAYS	14	(8.2)
1542 - 1625 DAYS	5	(2.9)
> 1625 DAYS	1	(0.6)

Adalimumab has a number of expected adverse events based on the experience in adult RA, many of which are related to the mechanism of action, namely the inhibition of TNF-α, an important arm of host defenses against infections and malignancies. In the clinical trials in JRA the safety profile was similar to that seen in adults with a few exceptions. Elevations in CPK were seen in a number of children. In addition, a greater proportion of children developed antibodies to adalimumab and there was a higher rate of non-serious hypersensitivity reactions.

6.3.2. Safety findings from submitted clinical trials

There were no deaths in the adalimumab trial in JRA. A total of 34 of the 171 subjects developed SAE's during the various phase of the trial experiencing a total of 52 events. Of these 52 events, there were 8 serious infections (2 cases of H. Zoster, 1-H. Simplex, 1-pharyngitis, 1-urinary tract infection, 1-pneumonia, 1-bronchopneumonia, 1 viral infection) and 3 cases of appendicitis. There was no other pattern of SAE's that suggested a relationship to adalimumab. Concerning the serious infections, none were unexpected based on what is currently described in the adalimumab package insert and none were opportunistic in nature. There was no pattern to suggest a higher risk of serious infection in patients receiving MTX combination therapy as compared to patients receiving adalimumab alone.

Adverse events leading to dropout were infrequent and included leucopenia, neutropenia and liver enzyme elevations, adverse events known to be associated with both adalimumab and with the MTX many study subjects were taking concomitantly.

Adverse events that were observed during the trial that may be related to adalimumab treatment include injection site reactions, which were seen in over 40% of patients in the open-label lead-in phase and decreased somewhat in later stages. Injection site reactions were not severe and did not preclude continued administration of adalimumab. A variety of infections were observed, prominently herpes simplex and herpes zoster virus infections. Herpes simplex infections were seen in approximately 4% of adalimumab-treated patients in the open-label lead-in and double-blind phases and 3-4% in the body surface area-based dosing portion of the extension trial. Allergic hypersensitivity reactions were seen in approximately 5-7% of patients and were not severe or serious.

Severe adverse events that were seen in the trial include neutropenia, various infections, liver enzyme elevations and a case of myositis. There was a single case of sporadic seizures in a 7 year old girl with no history of seizures and no other explanation for seizures. The case of myositis occurred in an 11 year old girl who developed CPK elevations up to 1055 U/L (normal range 18-187 U/L). She had a previous history of muscle weakness. The CPK normalized after adalimumab was stopped. The patient was able to resume adalimumab. She had several subsequent episodes of CPK elevation but none exceeded CTC grade 2. One additional patient developed myositis that was not considered severe. That patient developed a CPK of 456. He was able to continue study treatment.

Further investigation of CPK elevation revealed that more than 10% of patients treated with adalimumab develop mild elevations in CPK (less than 2.5X ULN). Severe elevations in CPK were observed in 5 children after prolonged treatment. In all but 1 case the CPK subsequently returned to normal. Adalimumab treatment was continued in most cases.

At the request of the Agency, the applicant carried out a post hoc analysis of hypertension that defined hypertension as 3 separate instances of a systolic (SBP) or diastolic blood pressure (DBP) exceeding the 95th percentile at any time during the study (Table 5). The clinical reviewer, Dr. Lapteva, notes that 14 out of 170 subjects with normal BP at the 2 pre-treatment visits had SBP or DBP exceeding the 95th percentile during the study and 6 patients had BP elevations on 3 consecutive visits. The strength of this potential safety signal of hypertension must be evaluated in view of the fact that 1) hypertension is fairly common in the enrolled patient population (40 of 170, or 24%); 2) this patient population is predisposed to hypertension by virtue of their receipt of predisposing medications such as NSAID's and corticosteroids; 3) the proportion of children starting as hypertensive who become non-hypertensive during the trial (14 out of 40, or 35%) is higher than the proportion who start normotensive who become hypertensive during the trial (14 of 112, or 12%); 4) mean blood pressure showed no significant rise during the trial (table 46 of Dr. Lapteva's review) and 5) there was no pattern of hypertension reported as an adverse event during the trial. Taken together these data suggest that this patient population is predisposed to hypertension and that there is considerable variability in blood pressure measurements from visit to visit. The data do not indicate an association of hypertension with adalimumab.

Table 5: Proportion of subjects meeting criteria for HTN and pre-HTN during the study according to the post-hoc analysis

PRE-DOSE	POST-DOSE			
	HTN	Pre-HTN	Normal BP	Total
HTN	26/45(58%)	12/71(17%)	2/54 (4%)	40
Pre-HTN	5/45(11%)	9/71(13%)	4/54(7%)	18
Normal BP	14/45 (31%)	50/71(70%)	48/54(89%)	112
Total	45/170 (26.5%)	71/170 (42%)	54/170 (32%)	170

6.3.3. Safety update

The results of the safety update are included in the discussion above.

6.3.4. Immunogenicity

Despite the fact that adalimumab is a recombinant human antibody it is nonetheless immunogenic. In adults with RA 1% of patients receiving adalimumab in combination with MTX develop anti-adalimumab antibodies (AAA), compared to 12% of patients receiving adalimumab monotherapy. In children with JRA, 6% of patients receiving MTX in combination with MTX developed AAA, compared to 26% receiving adalimumab alone. These data suggest a higher rate of immunogenicity in children compared to adults.

AAA may be expected to affect clearance as well as safety and efficacy of adalimumab. The data in children with JRA indicate that among children developing AAA trough levels of adalimumab declined over time in the open-label, lead-in phase while adalimumab levels increased to week 16 in patients who did not develop AAA. In the open-label, lead-in phase, children developing AAA in the group receiving adalimumab alone had a gradual decline in pedi ACR 30 responses over time while patients who did not develop AAA had rising pedi ACR 30 response rates. These data indicate AAA increased the clearance of adalimumab and may also reduce efficacy. Immunologic reactions, including hypersensitivity reactions, were more frequent in patients who developed AAA than in patients who did not (table 51 of Dr. Lapteva's review).

6.3.5. Discussion of primary reviewer's comments and conclusions

The primary clinical reviewer determined that adalimumab treatment in children with JRA was associated with infections, injection site reactions, cytopenias, autoantibodies, immunogenicity, hypersensitivity, elevations in CPK and in liver enzymes, granuloma annulare and a single case of a new onset seizure disorder. She noted that all of these adverse events are already described in the current product label for adalimumab with the exception of elevations in CPK, granuloma annulare and seizure disorder. As CDTL I am in agreement that these events represent potential safety concerns.

The clinical reviewer also noted that there were no cases in the JRA study of other adverse events that have been associated with adalimumab in adults, including malignancies, autoimmune disorders, demyelinating disorders or congestive hear failure. However, since those events could still be seen postmarketing she recommended a registry to investigate the occurrence of these adverse events that may occur at low frequency or with longer duration of exposure.

6.3.6. Discussion of notable safety issues

There are no unresolved safety issues.

7. Advisory Committee Meeting

No advisory committee meeting was convened to discuss this application. It was judged that the data submitted were adequate to determine whether the risk/benefit relationship was favorable for adalimumab in the treatment of children with JRA.

8. Financial Disclosure

Based on the information submitted by the Applicant there were no financial conflicts of interest that would have the potential to bias the data.

9. Labeling

9.1. Physician labeling

No major issues have been raised at the time of completion of this CDTL memo. However, detailed consideration of the label were just beginning.

10. DSI audits

Three clinical site inspections are in the process of being conducted by DSI at the time of completion of this review. The results are currently unavailable.

11. Conclusions and recommendations

11.1. Regulatory action

Data from study DE083 provide substantial evidence that adalimumab is efficacious in reducing signs and symptoms of polyarticular JRA when given as monotherapy and when given in combination with MTX. In the open-label, lead-in portion of the study, 74% of children receiving adalimumab monotherapy had a pedi ACR 30 response by week 16 as did 94% of children receiving adalimumab in combination with MTX. In the double-blind, placebo-controlled randomized withdrawal phase a statistically significantly greater portion of patients flared when adalimumab was withdrawn compared to when it was continued. Adalimumab treatment was associated with improvement in all 6 of the core set variables. Improvement in signs and symptoms was observed within 2 weeks of initiation of treatment in the open-label lead-in. All subgroups of patients based on demographics or disease activity appeared to benefit.

The safety profile of adalimumab in children with JRA was generally similar to that seen in adults with RA. Several adverse events were observed in children that had not been seen previously in adults. These adverse events should be reflected in the product label. Overall, the risk/benefit relationship for adalimumab in JRA is positive.

This BLA supplement should be approved with appropriate modifications to the proposed package insert.

11.2. Safety concerns to be followed postmarketing

The most important safety concerns to be followed postmarketing are serious infections, malignancies and autoimmune disease.

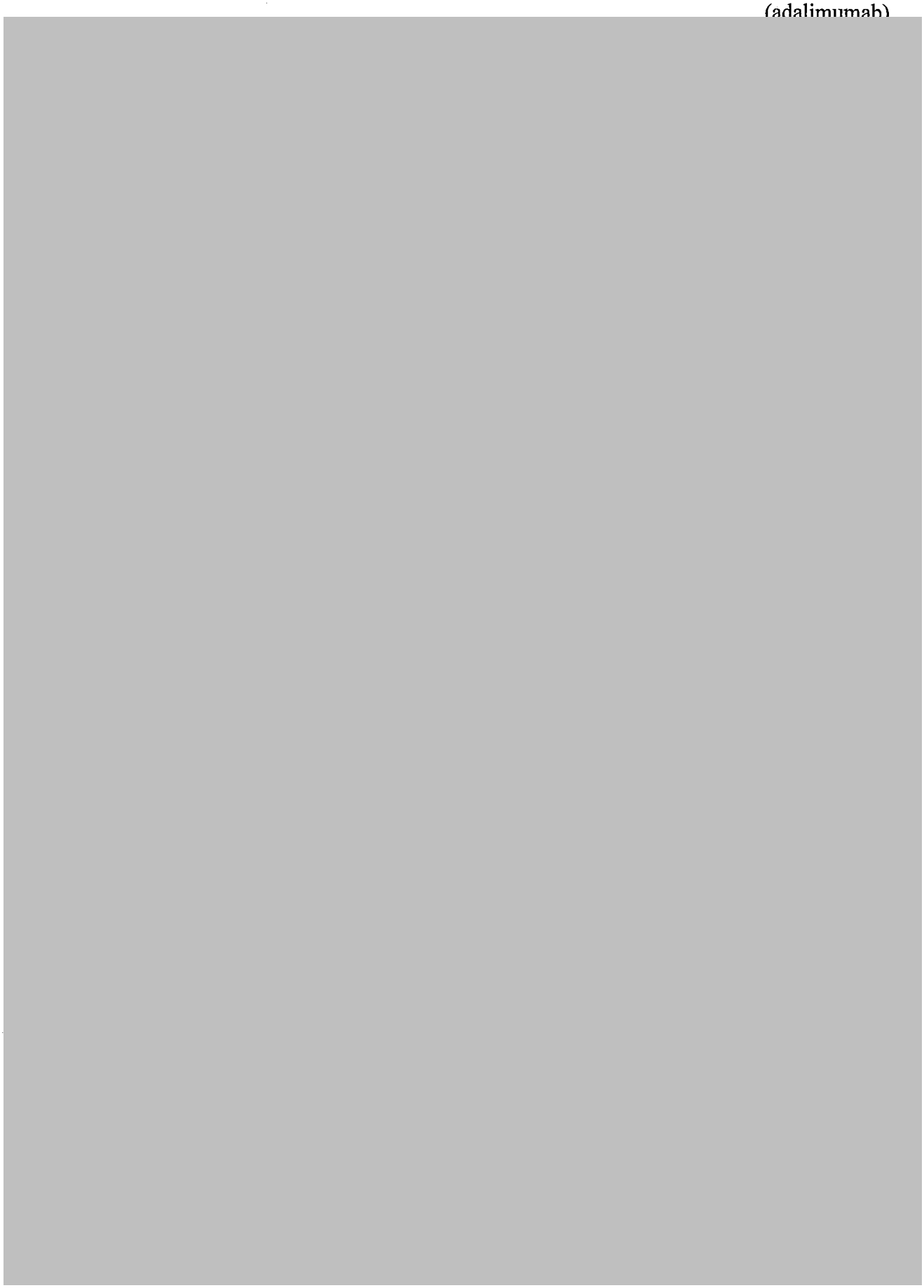
11.3. Postmarketing studies

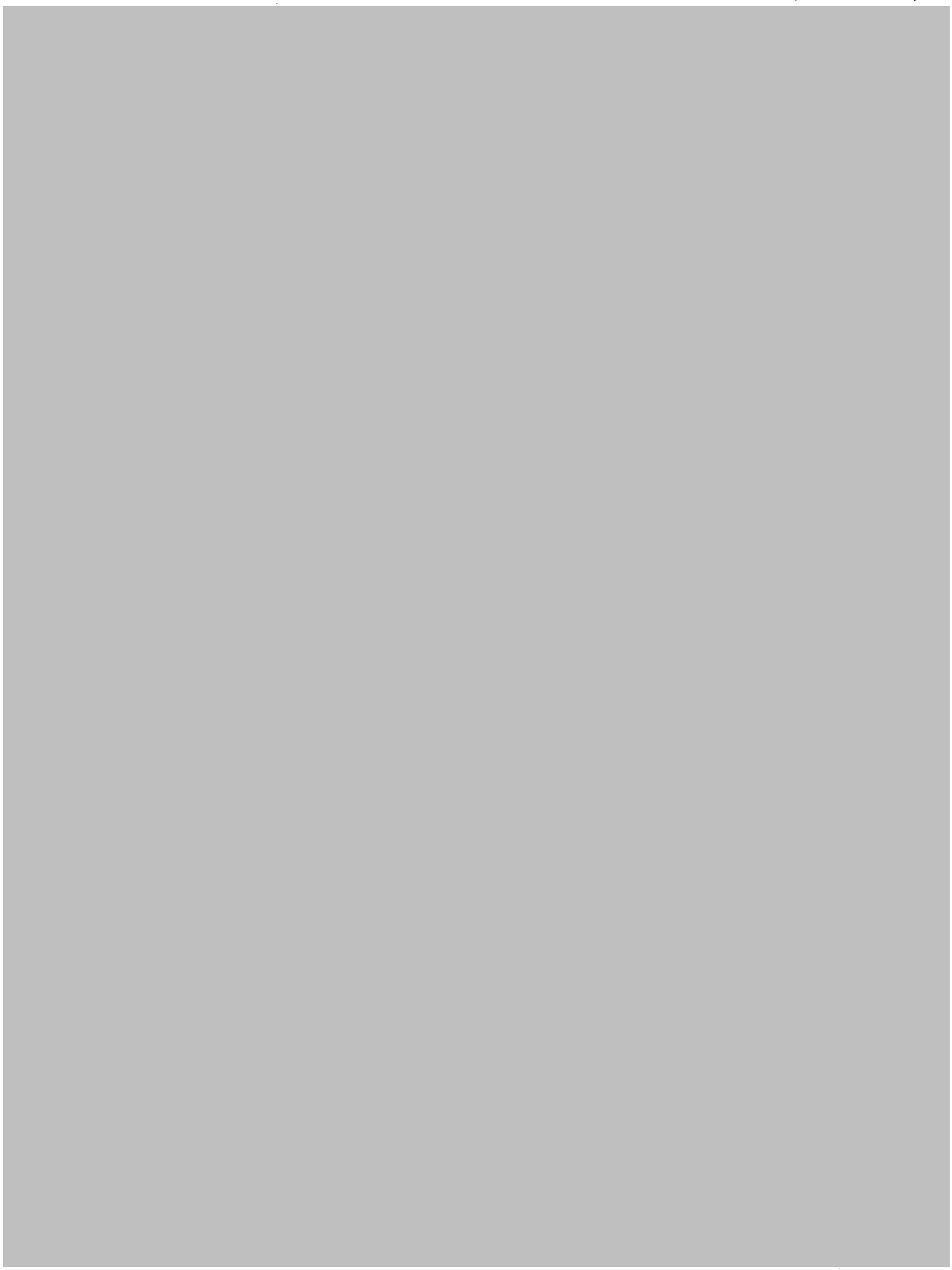
11.3.1. Required studies

There are no required studies.

11.3.2. Commitments (PMCs)

The applicant should conduct a postmarketing registry of children with JRA [redacted]





CLINICAL REVIEW

Application Type	sBLA
Submission Number	125057/114
Submission Code	Not applicable
Letter Date	April 26, 2007
Stamp Date	April 26, 2007
PDUFA Goal Date	February 24, 2007
Reviewer Name	Larissa Lapteva, M.D., M.H.S. 12/18/2007
Team Leader	Jeffrey Siegel, M.D. 9 5 12/18/07
Division Director	Bob Rappaport, M.D.
Review Completion Date	December 18, 2007
Established Name	Adalimumab
Trade Name	Humira
Therapeutic Class	Monoclonal antibody (MAb)
Applicant	Abbott Laboratories
Priority Designation	S
Formulation	human recombinant MAb to TNF-α
Dosing Regimen	20 mg SQ for children weighing <30kg and 40 mg SQ for children weighing ≥30 kg every two weeks
Indication	reducing signs and symptoms
Intended Population	poly-articular Juvenile Rheumatoid Arthritis

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This biologic license application (BLA) supplement is for the approval of adalimumab (Humira®) to be used as monotherapy or in combination with the disease modifying anti-rheumatic drug (DMARD) methotrexate (MTX) for reducing the signs and symptoms of moderately to severely active poly-articular course juvenile rheumatoid arthritis (JRA) in children 4-17 years of age not responding to other DMARDs. This supplement fulfills post marketing commitment (PMC) #1 from supplement BLA 125057/16.

Within the past decade, tumor necrosis factor (TNF) blockers, including adalimumab, used as monotherapy or in combination with MTX have revolutionized the approach to treatment of different kinds of inflammatory arthritis in adults. There is currently one TNF blocker approved for treatment of juvenile rheumatoid arthritis- etanercept (Enbrel®), a TNF-α receptor IgG1 Fc fusion protein. A double-blind, randomized-withdrawal, placebo-controlled study DE038 provides evidence for safety and efficacy of adalimumab, a recombinant, fully human monoclonal antibody with high affinity to TNF-α, in children with moderate to severe poly-articular course JRA

The safety profile of adalimumab in children with JRA appears overall similar to that seen in adults with RA. An increased incidence of infections, injection site reactions, uncommon cases of cytopenias, liver function test elevations, and formation of autoantibodies (anti-dsDNA) were observed in children treated with adalimumab. Additionally, adalimumab caused more non-serious hypersensitivity reactions and was more immunogenic in children compared to adults. Similar to adult studies, fewer subjects concomitantly treated with MTX developed anti-adalimumab antibodies compared to those treated with adalimumab alone. Elevations in the muscle enzyme, creatine phosphokinase, occurred in children treated with adalimumab, a laboratory abnormality not seen in adults. Certain expected serious adverse effects of adalimumab were not observed in this pediatric study. Incidences of these events remain unknown and should be further investigated in a post marketing safety study.

Given the observed efficacy of adalimumab, with cautious selection of treatment candidates and close monitoring for adverse effects, adalimumab will be a valuable addition to the treatment armamentarium for poly-articular course JRA and will likely decrease the disease burden and improve outcomes in children affected by juvenile rheumatoid arthritis.

Adalimumab should be approved for reducing signs and symptoms in children with moderately to severely active poly-articular course JRA with appropriate revisions to the proposed label.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

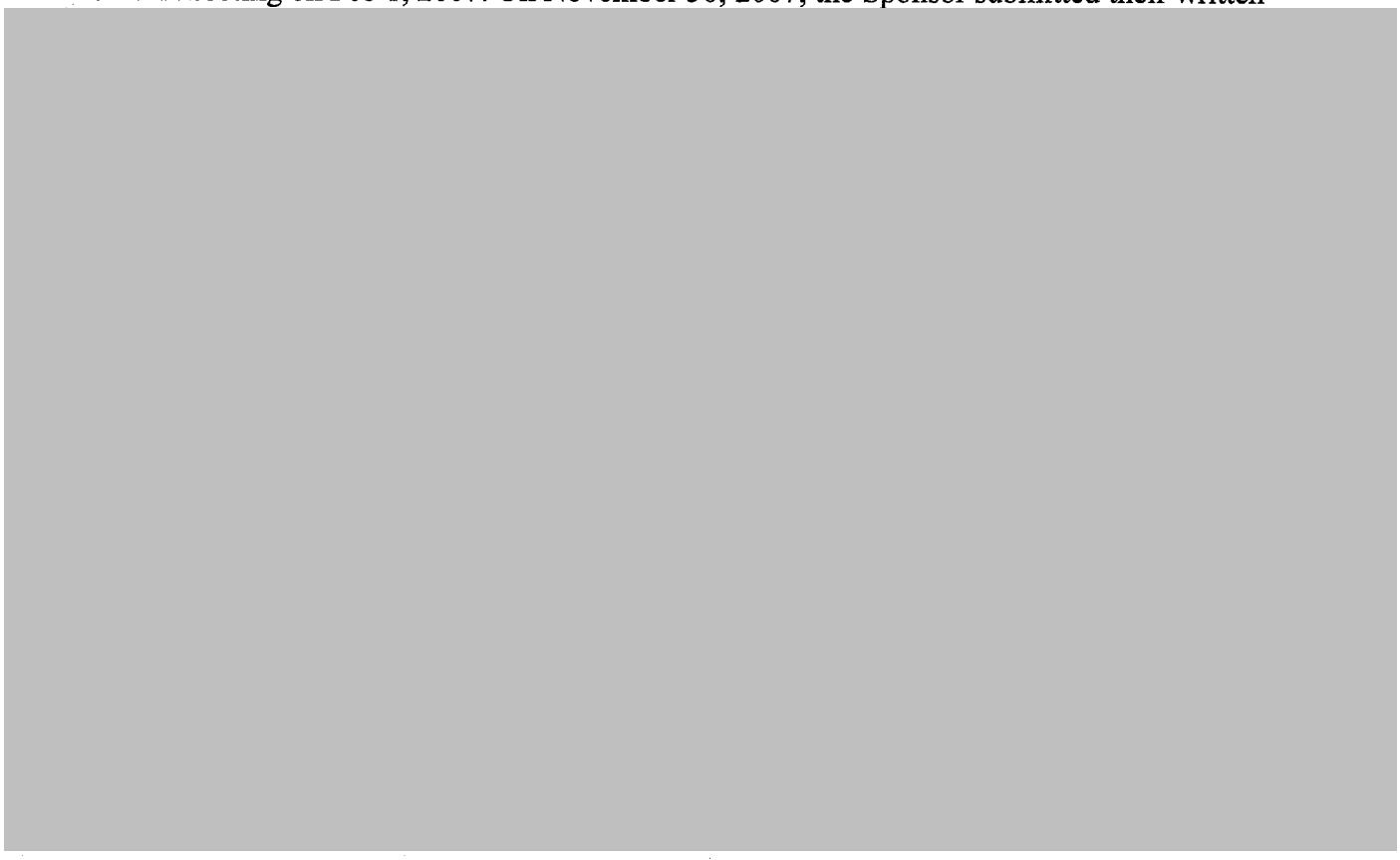
Humira® currently has a MedGuide that informs patients and parents about the potential risks of the product. Additionally, the product label provides complete available information on occurrences of adverse events associated with Humira®. Adverse events observed in the post marketing experience will be submitted to the Agency as part of standard pharmacovigilance.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

As indicated in Section 2.5 of this review, previous agreement about assembling a registry of the children treated with adalimumab was reached by the Division and the Sponsor during the pre-sBLA meeting on Feb 1, 2007. On November 30, 2007, the Sponsor submitted their written



[redacted]

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Adalimumab is a recombinant full-length monoclonal antibody containing exclusively human sequences with a high affinity for human TNF-alpha. Adalimumab is commercially available under the trade name Humira® and is currently indicated for treatment of adult rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn's disease. Adalimumab can be used alone or in combination with other non-biologic DMARDs.

The clinical development program for juvenile rheumatoid arthritis consisted of one study DE038 designed to evaluate the safety and efficacy of adalimumab in children aged 4-17 years with the poly-articular subtype of JRA (n=171). The study included four phases: the open-label lead in phase (OL-LI), the double-blind randomized withdrawal phase (DB), the open-label extension phase (OLE-BSA), and the open-label fixed dose phase (OLE-FD). Subject enrollment and analysis was performed in two strata: adalimumab alone (non-MTX stratum) and adalimumab administered concomitantly with methotrexate (MTX stratum).

In the first three phases of the study, adalimumab was administered based on body surface area at a dose of 24mg/m^2 of adalimumab subcutaneously (SQ) biweekly. In the OLE-FD phase, the children were treated with 20 mg of adalimumab SQ biweekly if their weight was <30 kg and with 40 mg of adalimumab SQ biweekly if their weight was $\geq$ 30 kg.

Upon completion of the OL-LI phase, only the enriched population of those who responded to treatment was eligible for randomization into the DB phase. The primary efficacy endpoint was a comparison of the proportions of subjects who flared in the DB phase upon either withdrawal (placebo group) or continuation (adalimumab group) of the study drug in the non-MTX stratum. Maintenance of the clinical benefit was then assessed in the OLE-BSA phase and OLE-FD phase. The design of treating the same cohort of subjects permitted an assessment of whether efficacy observed in OLE-BSA phase was maintained in OLE-FD phase.

1.3.2 Efficacy

Analysis of the primary and secondary endpoints provides statistically strong and consistent support for the efficacy of adalimumab in patients with moderate to severe poly-articular JRA. Subgroup and sensitivity analyses further support the clinical benefits of adalimumab.

Study DE038 provides the principal evidence demonstrating the clinical efficacy of adalimumab in patients with poly-articular JRA when used as a monotherapy or in combination with concomitant methotrexate (MTX). In this study, the American College of Rheumatology criteria for pediatric response (ACR pedi 30, 50, 70, 90) and occurrence of disease flares were used as endpoints for evidence of improvement of signs and symptoms and maintenance of the observed clinical benefits in children with poly-articlar JRA. After the initial 16 weeks of open-label treatment (n=171), ACR pedi 30 responses were observed in 74% of subjects treated with adalimumab alone and in 94% of subjects treated with the combination of adalimumab and methotrexate. Improvements in all parameters of ACR pedi 30 composite score were observed.

In the double-blind randomized phase of the study, only patients who showed improvement in their disease activity (at least ACR pedi 30 responders) were further randomized into either a placebo or an active treatment group within each stratum (n=133). Upon treatment withdrawal in the placebo groups and treatment continuation in the active treatment groups, the clinical benefits of adalimumab treatment were maintained resulting in statically significantly fewer flares in adalimumab-treated patients compared to the placebo-treated patients (43% vs 71% in the non-MTX stratum i.e. treatment with adalimumab alone and 37% vs 65% in the MTX stratum, i.e. treatment with the combination of adalimumab and MTX) observed after 32 weeks of treatment. The longevity of response was statistically significantly superior in subjects treated with adalimumab monotherapy or the combination of adalimumab and MTX than in subjects treated with placebo or MTX alone.

In the open-label extension phase of the study when all enrolled subjects (n=128) were treated with either adalimumab alone or the combination of adalimumab and MTX, the ACR pedi 30, 50, 70, and 90 responses were regained or maintained in the majority of adalimumab-treated patients. Modest decline in clinical responses was observed with long-term treatment.

The clinical benefit of adalimumab was further maintained after the patients were switched to the fixed dose regimen (n=106). The intention to treat analysis showed that of the patients treated with the combination of adalimumab and MTX who were switched to the fixed dose regimen (n=59), 90% were ACR pedi 30 responders before the dose switching and 85% patients

maintained the same level of response after 16 weeks of treatment with their designated fixed dose (20 or 40 mg subcutaneously biweekly). Of the patients treated with adalimumab monotherapy (n=47), 94% were ACR pedi 30 responders before the dose switching and 87% patients maintained the same level of response after 16 weeks of treatment.

Overall, the data presented in the Sponsor's submission support the claim that adalimumab, when used alone or in combination with MTX, reduces signs and symptoms in patients with moderate to severe poly-articular JRA [redacted]. Efficacy of adalimumab in children who failed previous treatment with a biologic product was not studied in study DE038.

1.3.3 Safety

A total of 171 pediatric patients were exposed to adalimumab in study DE038 and form the primary evidence of the safety of adalimumab in patients with poly-articular JRA. Adverse events related to adalimumab, similar to adult populations, included infections (primarily viral and upper respiratory infections), injection site reactions, cytopenias and liver function tests elevations. Throughout the study, serious infectious adverse events were observed in 4/86 (5%) of patients treated with adalimumab monotherapy and 3/85 (4%) of patients treated with the combination treatment.

Adalimumab was more immunogenic in children compared to adults, resulting in 6% (combination of adalimumab and MTX) and 26% (adalimumab monotherapy) of subjects developing anti-adalimumab antibodies. The respective rates of 1% with concomitant MTX and 12% with adalimumab monotherapy were previously observed in the adult RA population. No serious allergic or immunogenic reactions were reported in study DE038.

The rate of non-serious hypersensitivity reactions observed in children was also higher than in adults (5-7% in children vs 1% in adults).

The observed rate of autoanibodies formation reflected by anti-dsDNA seroconversion was at least 15/155 (10%) in previously negative anti-dsDNA patients after 48 weeks of treatment. No frank autoimmune syndromes were observed.

Isolated mild to moderate elevations of liver transaminases (primarily alanine aminotransferase) were observed in children with JRA exposed to adalimumab alone; liver function tests (LFT) elevations were more frequent among those treated with the combination of adalimumab and MTX.

Unlike in adults, over 10% of children exposed to adalimumab developed mild and moderate elevations of the muscular enzyme creatine phosphokinase. Severe elevations (over 1000 U/L) were observed in several patients in study DE038. Creatine phosphokinase decreased or returned to normal in all patients, the vast majority of the patients were able to continue adalimumab therapy without interruption.

No deaths, or other serious adverse events associated with adalimumab treatment including malignancies, opportunistic infections, mycobacterial infections, autoimmune syndomes, or central nervous system demyelinating disorders were observed in study DE038.

Isolated cases of granuloma annulare (2), new onset seizure disorder (1), and several cases of persistently elevated blood pressure were also observed in children treated with adalimumab.

Refer to Section 9.1 for recommendations on label changes.

Safety of adalimumab treatment in children who previously failed a biologic product was not studied in study DE038.

As recommended in the current product label, Humira® should not be given with live vaccines. This specific of product administration may affect pediatric population because vaccinations with live attenuated vaccines are among the obligatory vaccinations and revaccinations for young children according to the current recommendations of the Center for Disease Control and Prevention. To minimize possible delays or avoiding of the recommended vaccinations in young children with poly-articular JRA treated with Humira®, a statement that pediatric patients of appropriate age should be offered vaccinations or re-vaccinations with live attenuated vaccines whenever feasible prior to treatment with adalimumab should be added to the product label.

1.3.4 Dosing Regimen and Administration

The recommended dose of adalimumab for administration is 20 mg of adalimumab subcutaneously (SQ) biweekly for children weighing <30 kg and 40 mg of adalimumab SQ biweekly for children weighing ≥ 30 kg. This dose was studied in the fourth phase of the study – open label extension phase with fixed regimen (OLE-FD). The children who responded to adalimumab treatment in the previous phases of the study were able to maintain their clinical responses after 16 weeks of treatment with the fixed doses. Upon review of adverse events in children whose dose of adalimumab was increased, more injection site reactions were observed with increase in adalimumab exposure in the children previously treated with adalimumab, likely owing to an increase in the injected volume of the product.

The proposed dose of adalimumab appears to have an adequate risk benefit ratio (also refer to Clinical Pharmacology review by Dr. Garnett).

The dosing experience based on body surface area is limited with children <15 kg of weight. The dosing experience with the fixed dose regimen is currently unavailable for children <20 kg of weight, since the smallest child entering the OLE-FD phase weighed 20 kg.

1.3.5 Drug-Drug Interactions

Specific drug-drug interactions were not formally studied in this pediatric clinical development program. In adults, the biologic TNF blocker class of drugs is not recommended to be used

concomitantly with other biologics such as anakinra, abatacept and rituximab. Given that there are no data to complete a risk benefit assessment of adalimumab in combination with other biologic DMARDs in children with poly-articular JRA, this reviewer recommends that adalimumab not be used in combination with other biologic therapies until there are adequate supporting data.

2. INTRODUCTION AND BACKGROUND

Juvenile Rheumatoid Arthritis (JRA) is one of the most common rheumatic diseases in childhood and a leading cause of childhood disability. There are three subtypes of JRA that usually characterize the clinical course at onset of the disease: pauciarticular (60%), polyarticular (30%) and systemic (10%). The subtype of JRA may change during the disease course; thus, children with pauci-articular or systemic subtypes at presentation may evolve into polyarticular subtype later in their disease course. Study DE038 investigated the effect of treatment with adalimumab (Humira®) in children meeting ACR criteria for the poly-articular subtype of JRA at the time of study enrollment.

2.1 Product Information

Adalimumab (Humira®) is a recombinant human IgG1 monoclonal antibody that is specific for human tumor necrosis factor (TNF)-α and contains exclusively human sequences. It belongs to the group of biologic products known as TNF blockers since adalimumab neutralizes TNF-α, thus promoting anti-inflammatory effects in vivo.

In the United States, adalimumab (Humira®) was first approved for treatment of adult RA on December 31, 2002; subsequently, it was approved for other indications including treatment of psoriatic arthritis (October 2005), ankylosing spondylitis (July 2006), and Crohn's disease (February 2007).

In this BLA supplement, the Sponsor Abbott Laboratories proposes to use adalimumab for the indication of treatment of poly-articular JRA in children and adolescents age 4-17 years. The proposed dose is a fixed regimen of 20 mg for children weightng <30 kilograms and 40 mg for children weighing ≥ 30 kilogram administered subcutaneously every other week.

2.2 Currently Available Treatment for Indications

The major categories of currently available non-biologic pharmacological treatments for JRA include: (1) non-steroidal anti-inflammatory drugs (most commonly prescribed naproxen and ibuprofen, as well as aspirin (salicylates)); (2) non-biologic DMARDs such as methotrexate, hydroxychloroquine, cyclosporine, azathioprine, sulfasalazine, gold, etc; (3) oral and parenteral corticosteroids.

There are two other products from the group of TNF blockers, infliximab (a chimeric human and mouse monoclonal IgG1 antibody that binds soluble and membrane bound TNF-α; trade name Remicade®) and etanercept (a divalent soluble p-75 TNF-α -receptor IgG1 Fc fusion protein; trade name Enbrel ®). Both of these products have been approved for treatment of adult RA; the latter was also approved for treatment of poly-articular JRA.

2.3 Availability of Proposed Active Ingredient in the United States

Adalimumab (Humira®) is currently marketed in the United States after it was originally approved for treatment of adult RA on October 31, 2002. Humira® is available in a single-dose prefilled pen or syringe containing 40mg/0.8ml for biweekly subcutaneous injections.

2.4 Important Issues With Pharmacologically Related Products

The major safety concerns with TNF blockers include: increased risk for all kinds of infections, including opportunistic infections (e.g mycobacterial, fungal) and reactivation of latent viral infections (hepatitis B, herpetic infections), uncommon cases of demyelinating disoders, serious blood dyscrasias, severe allergic reactions, and injection site reactions.

Additionally, higher incidences of malignancies (lymphomas, non-melanoma skin cancers) have been observed in patients receiving monoclonal antibodies to TNF-α, adalimumab and infliximab, compared to control patients in clinical trials. In the controlled clinical trials with adalimumab (combined data from trials in RA, psoriatic arthritis, ankylosing spondylitis and Crohn's disease) an approximately 4-fold higher rate of non-melanoma skin cancers was observed in patients treated with Humira ® compared to control patients (Source: Humira® label). A recent large observational study showed an increased risk for development of non-melanoma skin cancers and melanoma in patients treated with biologics compared to general population[4]. Rare cases of aggressive hepatosplenic T-cell lymphoma occurred in adolescent and young adult patients with Crohn's disease treated with anti-TNF monoclonal antibody infliximab post marketing (Remicade® label, boxed warning).

The observed rate of lymphomas among patients treated with adalimumab (combined data from controlled and uncontrolled open-label clinical trials) was about 4-fold higher in adalimumab-treated patients compared to the general population (Humira® label). A meta-analysis of randomized placebo-controlled trials with infliximab and adalimumab showed evidence of an increased risk of malignancies in the patients treated with the monoclonal antibodies to TNF-α compared to the control groups[5]. One observational study demonstrated no increased risk of lymphoproliferative disorders[4] in patients treated with biologics compared to general population (US National cancer institute Surveillance, Epidemiology, and End Result, SEER database). However, safety analyses of adalimumab in global clinical trials and US post marketing surveillance of patients with RA demonstrated an increased incidence of lymphoma in adalimumab clinical trials (SIR 3.19 [95%CI 1.78-5.25]) over general population while using normal population rates from the SEER database as the comparison reference[6]. Whether the observed incidences solely indicate higher risks of lymphoma occurrence in association of adalimumab treatment or partly reflect the known predisposition to an increased risk for lymphoma in patients with rheumatoid arthritis remains to be seen in future prospective observational studies.

Other conditions that have been reported in association with TNF blockers, including adalimumab, are: 1) worsening of preexisting congestive heart failure (CHF) and cases of new onset CHF and 2) autoimmune reactions including lupus-like syndrome.

All of the above safety concerns are listed in the warnings and precautions section of the current adalimumab (Humira®) label. The warning about the risk of serious infections, TB reactivation, and other opportunistic infections is included as a boxed warning in the current Humira® label.

2.5 Presubmission Regulatory Activity

The current application is the Sponsor's submission of a pediatric study in a response to post marketing commitment (PMC) agreed to by the Sponsor upon approval of a supplemental application to expand the RA indication to include improvement of physical function on July 30, 2004. At the time, the PMCs stated in the supplemental approval letter were: (1) To continue Study DE038 and submit the final study report by March 2006 and (2) To evaluate the feasibility of conducting a study in patients age 0-4 years and, if appropriate, submit a pediatric study plan or request a waiver by March 31, 2007.

To meet PMC #1 the Sponsor conducted the DE038 study that originally included three phases: open-label lead in, double-blind randomized withdrawal, and open-label extension; the dosing in all three of these phases was calculated based on the body surface area of each individual patient. On April 25, 2006 the Agency and the Sponsor held a teleconference and agreed upon analysis methods for the statistical analysis plan of the double-blind portion of the DE038 study. Subsequently, the Sponsor proposed a fixed dose regimen based on body weight to be evaluated in the open-label portion of the study. On June 7, 2005 the Sponsor and the Agency held a teleconference and at that time an agreement was reached to convert the study participants in the open-label extension phase to a fixed dose regimen based on body weight (20 mg of adalimumab subcutaneously biweekly for children weighting <30 kg and 40 mg of adalimumab subcutaneously biweekly for children ≥ 30 kg). Consequently, the submitted DE038 study now consists of four phases: open-label lead in, double-blind randomized withdrawal, open-label extension treatment by body surface area, and open label extension treatment with fixed dose regimen based on weight.

To discuss PMC #2 a teleconference was held between the Agency and the Sponsor on February 2, 2005 [redacted]

A request for Orphan drug designation for JRA indication was submitted on January 6, 2005 and subsequently granted by the Agency on March 21, 2005.

A pre-sBLA submission type B meeting was held with the Sponsor on February 1, 2007 and several technical agreements about data submission were reached (see meeting minutes from Feb 1, 2007 meeting).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No outstanding CMC issues were found upon review of the application (refer to CMC review by Dr. Gurpreet Gill-Sangha). The manufacturing process and container closure for the new strength (20 mg/0.4 mL) added for the pediatric population was adequate and the same as for the approved adult (40 mg/0.8 mL) strength.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is based on data from clinical trials conducted by the Sponsor, Abbott Laboratories, submitted in the original submission of sBLA supplement #125057/114 and all related submissions for the period April 26- December 20, 2007.

4.2 Tables of Clinical Studies

Table 1 below summarizes the four phases of study DE038 that form the primary basis for this review.

Table 1. Study# DE038.

Phase	Duration	Number of subjects enrolled	Number of subjects completed
Open label Lead In (OL-LI)	16 weeks	171	159*
Double blind Randomized Withdrawal (DB)	32 weeks	133	128
Open label Extension with dosing based on Body Surface Area (OLE-BSA)	up to 136 weeks	128	106
Open label extension with fixed dosing (OLE-FD)	48 weeks	106	96

* subject # 5302 withdrew from the OL-LI phase of the study prior to its completion; therefore, n for OL-LI completers differs from n=160 originally reported by the Sponsor.

4.3 Review Strategy

The primary focus of this review is study DE038 that was conducted in the target pediatric population of children aged 4-17 years who had poly-articular JRA at the time of study participation (n=171). Study DE038 consisted of four phases: open-label lead in (OL-LI, 16 weeks), double-blind randomized withdrawal (DB, 32 weeks), open-label extension treatment by body surface area (OLE-BSA, duration varied for different patients; maximum duration was up to 136 weeks), and open label extension treatment with fixed dose regimen (OLE-FD, 48 weeks). The study was multi-center and was conducted in multiple sites in both Europe and the United States.

The first three phases of the study were conducted with a dose of adalimumab of 24mg/m^2 of body surface area as every other week (eow) subcutaneous (SQ) injections; the fourth phase was designed to give 20 mg SQ injections eow to children weighing <30 kg and 40 mg SQ injections eow to children weighing ≥ 30 kg.

The main efficacy conclusions were drawn from the results of the double-blind randomized withdrawal phase of the study. They were further supported by the efficacy results characterizing the onset of clinical benefit from the OL-LI phase and the maintenance of response in the OLE-BSA and OLE-FD phases.

The review of safety was based on safety assessments for all exposed subjects from study DE038 (n=171). The safety data were evaluated for serious adverse events (SAEs), deaths, adverse events (AEs), changes in laboratory parameters, vital signs, any potential safety signals, as well as for the specific safety concerns associated with the class of TNF-blockers, namely: infections, opportunistic infections, malignancies, allergic and skin reactions, autoimmunity, and immunogenicity.

A biostatistics review of the data was conducted by Dr. Joan Buenconsejo.

4.4 Data Quality and Integrity

In general, the data quality and integrity were adequate. The amount of missing data was negligible and did not interfere with reaching conclusions on efficacy and safety. Overall, there were no major issues regarding data quality and integrity of the study.

4.5 Compliance with Good Clinical Practices

Study DE038 was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practices (GCP). The study was conducted in compliance with the study protocol. Informed consent, protocol, amendments, the Investigator's Brochure,

administrative letters, and other necessary documents received Institutional Review Board and Independent Ethics committee approval prior to implementation.

4.6 Financial Disclosures

Financial disclosure was reviewed and deemed to be complete. No financial interest was reported that would be expected to influence the integrity of the overall study results or influence any of the findings.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Dr. Christine Garnett performed the analysis of the clinical pharmacology of adalimumab in patients with JRA for this application. Since there was a dose switch from the dosing based on body surface area to the fixed dosing regimen, the main focus of Clinical Pharmacology review was evaluation of the adequacy of the proposed fixed dose regimen and the proposed cut off weight of 30 kg for different dosing (20 mg vs 40 mg dose). Key conclusions from Dr. Garnett's review are as follows:

1) For the 50 subjects who had a dose increase to 40-mg *eow*, the mean trough adalimumab concentrations increased from 5.0 ± 5.4 μg/ml (BSA dosing) to 7.0 ± 5.3 μg/ml (OLE-FD phase) for adalimumab monotherapy and from 6.2 ± 4.6 μg/ml (BSA dose) to 6.8 ± 6.9 μg/ml (OLE-FD phase) for the combination of adalimumab and methotrexate.

2) The dose proposed by the Sponsor and the cut off weight of 30 kg for different dosing is acceptable.

3) The Sponsor's population PK model did not adequately describe the observed adalimumab data. The model under-predicted high adalimumab concentrations and over-predicted low concentrations. The median % prediction error within each quartile of observed concentrations is +98%, -5%, -23% and -34%. Consequently, it was recommended that observed steady state trough serum concentrations be used to describe the exposure to adalimumab following administration of adalimumab 20-mg SC every other week to subjects weighing less than 30 kg and adalimumab 40-mg SC every other week to subjects weighing 30 kg or more (refer to Dr. Garnett's review for detailed analysis of clinical pharmacology of adalimumab in children with JRA).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor's proposed indication is reducing signs and symptoms of moderately to severely active poly-articular subtype juvenile rheumatoid arthritis in patients

6.1.1 Methods

The Sponsor submitted the results of study # DE038 that included four phases of treatment of one cohort of subjects with moderate to severe poly-articular subtype of JRA. The four phases of the study are also described in Section 4.1 and included the open-label lead in phase (OL-LI), the double-blind randomized withdrawal phase (DB), the open-label extension phase with dosing administered based on body surface area (24mg/m^2 SQ biweekly, OLE-BSA), and the open-label fixed dose phase with fixed dose regimen (OLE-FD). In the OLE-FD phase children were treated with 20mg of adalimumab SQ biweekly if their weight was <30 kg and with 40 mg of adalimumab SQ biweekly if their weight was $\geq$ 30 kg. Upon completion of the OL-LI phase only the enriched population of ACR Pedi 30 responders was eligible for randomization into the DB phase. The primary efficacy endpoint was a comparison of the proportions of subjects who flared in the DB phase upon either withdrawal (placebo group) or continuation (adalimumab group) of the study drug. Subject enrollment and analysis was performed in two strata: adalimumab alone and adalimumab administered concomitantly with methotrexate (MTX). Maintenance of the clinical benefit was then assessed in the OLE-BSA phase and OLE-FD phase.

6.1.2 General Discussion of Endpoints

Two major endpoints were used in this study: disease flare (primary efficacy endpoint) and pediatric ACR responder criteria (secondary efficacy endpoint). The pediatric ACR responder criteria could be further subcategorized by degree of improvement which in this study included ACR Pedi 30, 50, 70, and 90 responder categories. Both major endpoints were composite scores constructed on the same JRA core set criteria used for this study.

<u>The JRA core set criteria in study DE038:</u>
-number of active joints (based on 66 joints assessment)
-number of joints with limitation of motion (based on 69 joints assessment)
-physician's assessment of JRA disease activity (PhGA, VAS 1-100)
-subject or parent assessment of JRA disease activity (PGA, VAS 1-100)
-childhood disability Health Assessment Questionnaire (DICHAQ)
-C-reactive protein (CRP)*.

The JRA core set criteria consist of 6 components (as above) originally designed and validated to reflect different aspects of JRA. The original definition included erythrocyte sedimentation rate

(ESR)* as the laboratory criterion for measurement of inflammation, however, similarly to the adult ACR scoring, C-reactive protein (CRP) could substitute this parameter at discretion of investigators[1]. The number of involved joints is assessed by 2/6 variables in the JRA core set criteria which makes this scoring system particularly suitable for assessment of polyarticular subtype of JRA, as in this study.

Definition of ACR pediatric (ACR pedi) 30/50/70/90 in study DE038:

1) Definition of ACR pedi 30:
- ≥ 30% improvement in at least 3 out of 6 JRA core set criteria AND
- ≥ 30% worsening in not more than 1 out of 6 JRA core set criteria.

ACR pedi 50/70/90 were defined similarly to ACR pedi 30 except using improvement percentage of 50, or 70, or 90 respectively while the worsening percentage remained at 30.

The JRA core set criteria used in the context of ACR pedi 30/50 /70 responder criteria have been validated and previously used in clinical trials in JRA populations.

Definition of JRA disease flare in study DE038:
- ≥ 30% worsening in at least 3 out of 6 JRA core set criteria and a minimum of 2 active joints AND
- ≥ 30% improvement in not more than 1 out of 6 JRA core set criteria.

If used to define disease flare, physician's and parents' global assessments had to change by at least 30% on a scale of 0-100 (refer to Section 6.1.3 for discussion).

The randomized withdrawal design, JRA core set criteria, ACR pedi 30/50/70 response criteria and similar definition of disease flare have all been previously accepted by FDA in JRA clinical trials. All the above endpoints and their definitions (except PedACR 90) were stated in the statistical analysis plan (SAP) for study DE038 and agreed upon in April 2005. The modification of the flare definition and addition of ACR pedi 90 criterion were submitted to the Agency in the subsequent protocol amendments.

In this review, ACR pedi 30, 50, 70, and 90 will be referred to as PedACR 30, 50, 70, and 90, respectively.

6.1.3 Study Design

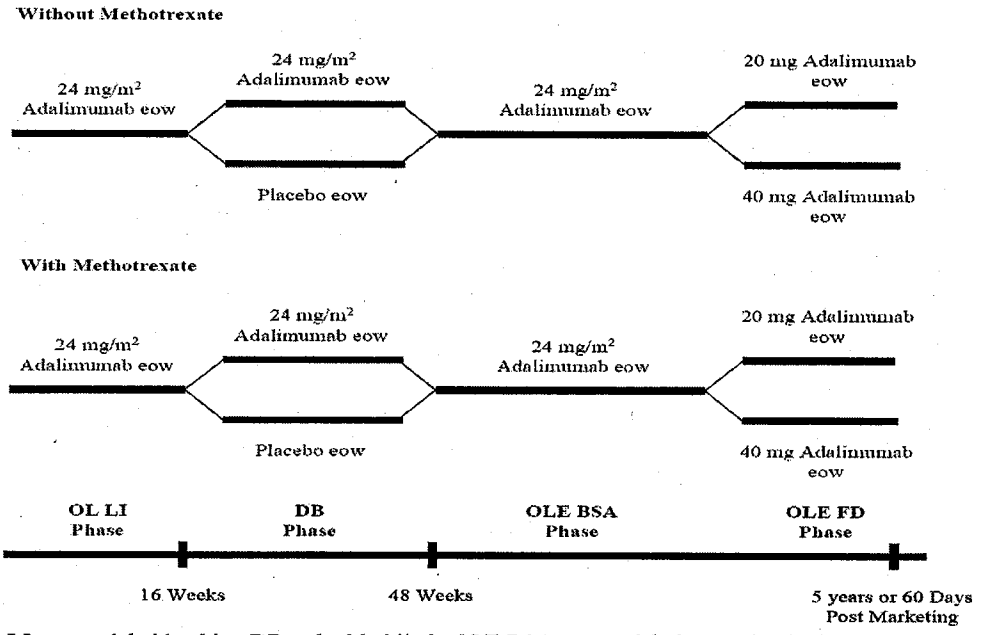
Study DE038 was a Phase 3, multi-center, double-blind, placebo-controlled, parallel-group, stratified by concomitant methotrexate (MTX) treatment, randomized withdrawal study in children 4-17 years old with polyarticular JRA (regardless of the type of JRA at onset). Phases of the study and durations are shown in Table 2; the study design is shown in **Figure 1**.

Table 2. Four phases of Study DE038.

Phase	Duration

Open label Lead In	16 weeks
Double blind	32 weeks
Open Label Extension with dosing based on Body Surface Area	up to 136 weeks
Open Label Extension with Fixed Dosing	48 weeks

Figure 1.
Study Design for study DE038



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

Source: Sponsor's Figure 1, p 162, CSR

Inclusion Criteria:

1. Subjects were to have a diagnosis of polyarticular course JRA aged 4 to 17 years by the ACR criteria. Disease onset may have been systemic, polyarticular, or pauciarticular. If the disease was systemic onset, then the subjects were to be free of any systemic JRA manifestations for at least three months before the time of qualification.

2. At the time of study screening, the subject was to have had continuing active disease defined as ≥ 5 swollen joints and ≥ 3 joints with limitation of motion (LOM). These joints are not mutually exclusive.

3. Subjects were to have been either naïve to MTX, inadequate responders to MTX, or intolerant to MTX. Intolerance to MTX was to be defined by the subject's physician. MTX was to have been maintained 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. This MTX dose was to have been maintained for a minimum of three months prior to Screening.

4. Duration of disease was not limited, but was to have been long enough for a subject to have been given an adequate trial of NSAIDs.

5. Subjects were not to have received other DMARDs including penicillamine, hydroxychloroquine, sulfasalazine, oral or injectable gold, cyclosporin; or intravenous (IV) immunoglobulin (IV Ig); or cytotoxic agents, for at least four weeks prior to receiving the 1st dose of study drug. Subjects currently on one or more of these DMARDs were to have demonstrated active disease (defined above) prior to a minimum four weeks (28 days) washout of all DMARDs.

6. Subjects who were refractory to MTX after three months of treatment were to have demonstrated active disease (defined above) prior to enrollment in the OL LI phase.

7. Subjects were not to have received an intra-articular glucocorticoid injection within four weeks (28 days) prior to enrollment into the study.

8. Subjects were to have had good venous access and stable hematocrit $\geq$ 24%.

9. All sexually active male and female study participants were to have been practicing adequate contraception. Post-pubertal females were to have had a negative serum pregnancy test no greater than 10 days prior to the first dose of study drug. If the first dose of study drug was greater than 10 days from the date the negative serum pregnancy test was performed, a urine pregnancy test was to have been done at the Baseline visit.

10. Parent or guardian was to have voluntarily signed and dated an informed consent form, approved by an IRB/IEC, after the nature of the study had been explained and the subject's parent or legal guardian has had the opportunity to ask questions. The informed consent was to have been signed before any study-specific procedures were performed or before any medication was discontinued for the purpose of this study. Pediatric subjects were to be included in all discussions in order to obtain verbal or written assent.

11. Parent or legal guardian was to have been willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subject's diary.

Exclusion Criteria:

1. Pregnant or nursing female.

2. Functional class IV by ACR criteria.

3. Demonstration of clinically significant deviations in any of the following laboratory parameters:
- Platelet count < 100,000/mm3
- Total white cell count < 4000 cells/mm3
- Neutrophils < 1000 cells/mm3
- AST or ALT > 2 x the upper limit of normal (ULN) or serum bilirubin > 2x ULN
- Glomerular filtration rate (GFR) of <90 mL/min/1.73 m2 BSA [GFR (mL/min/1.73 m2 BSA) = 0.55 x height (cm)/plasma creatinine (mg/dL)]
- Hematocrit < 24 %

4. Known positive human immunodeficiency virus (HIV) status.

5. Subjects who had positive serology results for hepatitis B surface antigen or hepatitis C antibody.

6. Subjects who had previous treatment with anti-TNF, anti-CD4, DAB-IL-2, IL1ra, or other investigative biological agent.

7. Subjects who had been administered a live or attenuated vaccine within three months prior to study drug administration.

8. Subject who had joint surgery within two months prior to the screening evaluation.

9. Subjects who had any ongoing chronic or active infection or any major episodes of infection requiring hospitalization or treatment with IV antibiotics within 30 days or oral antibiotics within 14 days prior to the Screening evaluation.

10. Subjects who had intra-articular, intramuscular or IV administration of corticosteroids within four weeks prior to enrollment.

11. Subjects who had treatment with any other investigational agent within 30 days or 5 half-lives of the agent, whichever was longer, prior to the screening evaluation.

12. Subjects who had a history of a central nervous system (CNS) neoplasm, active CNS infection, CNS demyelinating disease, degenerative neurological disease or any progressive CNS disease.

13. Subjects who had poorly controlled diabetes.

14. Subjects who had a history of active tuberculosis (TB) or listeria infection.

15. Subjects who had a history of malignancy with the exception of successfully treated non-metastatic basal cell carcinoma of the skin.

16. Subjects who had any concurrent medical condition that would, in the Investigator's opinion, compromise the subject's ability to tolerate study drug or would make the subject unable to cooperate with the protocol will be excluded.

17. Subjects who had a history of/or current psychiatric illness that would interfere with ability to comply with protocol requirements or give informed consent.

18. Subjects who had a recent history of alcohol or drug abuse within the past six months that would interfere with ability to comply with protocol requirements.

19. Subjects who had an inability to comply with the study requirements.

Stratification by concomitant methotrexate (MTX)

At the baseline OL-LI phase visit all subjects were enrolled in two strata: MTX stratum (combination of MTX and adalimumab) and non-MTX stratum (adalimumab only). The strata were maintained throughout all four phases of the study. For subjects enrolled within the MTX stratum, the dose of MTX was to be stable for at least three months prior to the screening visit. For subjects enrolled in the non-MTX stratum, prior MTX use was to have been discontinued at least two weeks prior to the baseline visit. Subjects stratified to the non-MTX stratum were to have been naïve or intolerant to MTX.

Other concomitant medications:

Stable doses of NSAIDs, low dose of corticosteroids ($\leq$ 0.2 mg of prednisone per kilogram per day, up to a maximum of 10 mg per day) or both were permitted. DMARDs, other than MTX, were discontinued 4 weeks before receiving the first dose of the study drug (adalimumab) in the OL-LI phase.

Intra-articular and soft-tissue corticosteroid injections were not permitted for four weeks prior to study enrollment. No corticosteroid injections were permitted during the OL-LI phase. One intra-articular and/or soft-tissue corticosteroid injection was permitted after the subject was randomized into the DB phase. However, the joint that was injected was considered non-evaluable for 3 months.

Treatments administered:

At the beginning of the OL-LI phase, subjects were stratified into two groups based on MTX use prior to enrollment. Subjects received adalimumab at 24 mg per m^2 BSA (up to a maximum total body dose of 40 mg) every other week (eow) subcutaneously for a period of 16 weeks. At Week 16, PedACR30 responders were randomized within their stratum to receive either active drug or matching placebo. The first dose of the DB medication was given at the Week 16 visit.

Subjects who 1) flared during the DB phase of the study, or 2) completed the DB phase of the study, were offered to enter the open label extension phase (OLE-BSA). Subjects who entered the OLE-BSA phase received adalimumab at 24 mg per m^2 BSA (up to a maximum total body dose of 40 mg) every other week prior to switching to a fixed dose (FD) regimen in the open label extension fixed dose (OLE-FD) phase. Upon consenting, subjects were enrolled into the OLE-FD phase where children who weighed < 30 kg received 20 mg eow and children who weighed ≥ 30 kg received a dose of 40 mg eow subcutaneously. Subjects choosing not to continue into the OLE-FD phase were terminated from the study. After switching to the fixed dose regimen at OLE-FD baseline, no dose adjustments were allowed during the OLE-FD phase. Once in the OLE-FD phase, the subject was allowed to continue up to 176 weeks.

Pre-specified primary efficacy endpoint (measured during the DB phase of the study):

Definition of JRA flare:
- ≥ 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

A percent change was calculated as 100x (value-baseline)/baseline, where baseline was based on appropriate visit. An improvement in ≥ 30% was defined as a percent change from open-label baseline less than or equal to -30 and worsening of ≥ 30% was defined as a percent of change from baseline greater or equal to 30. The DB baseline visit assessment was used as the reference point for the disease flare calculation.

Physician's and parents' global assessments had to change by 30% from baseline to meet the threshold for the definition of flare. Such criterion was a deviation from the originally proposed criterion for change in global assessments (change by at least 2 units on a scale of 0-10), and submitted as a protocol amendment in July 2003. This change permitted to count lesser worsening in the global assessments for the flare definition compared to the original 2 unit criterion. This new criterion allowed rescuing of the placebo-treated subjects upon less

pronounced worsening of their disease, but also might have led to an increase in the number of counted flares in both strata.

Pre-specified primary efficacy objective:

To determine and compare disease flare rate in adalimumab-treated subjects and placebo-treated subjects in the polyarticular JRA population of patients who had previously responded to adalimumab treatment.

The pre-specified primary analysis was a comparison of the proportions of subjects who flared in both groups (adalimumab vs placebo) in the non-MTX stratum on the intention to treat (ITT) population denominator. The Chi-square test was employed for the comparison of proportions.

The following JRA core set of variables listed below were used to determine disease flare (also see Section 6.1.2):
- Physician's Global Assessment of subject's disease severity by visual analog scale (VAS, 0-100mm),
- Parent's Global Assessment of subject's overall well-being (VAS, 0-100mm),
- Number of active joints (joints with swelling not due to deformity or joints with limited range of motion (LOM) and with pain, tenderness or both),
- Number of joints with LOM,
- DICHAQ (disability index childhood health assessment questionnaire),
- CRP (C-reactive protein).

As was pre-specified by the Sponsor and agreed by the Agency, the 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 used for response or flare calculation.

The pre-specified sensitivity analyses for handling of dropouts for the primary analysis included:

1. Imputation method #1 (pre-specified primary analysis). 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.
2. Imputation method #2. This imputation will be the same as imputation#1 except for the subjects in the placebo group who discontinue the study because of the primary reason other than flare (for example, adverse events); these subjects will be considered as non-flared.
3. Imputation method #3. This imputation was to be done using the last observation carried forward (LOCF) approach for the disease flare.

Sample size calculation:

The sample size was calculated based on the assumption that a difference in the proportion of subjects between the placebo and the active adalimumab groups in the non-MTX stratum who

would experience disease flare would be 40% assuming a flare rate of 70% in the placebo group vs. a flare rate of 30% in the adalimumab group. It was further estimated that assuming 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 group within the appropriate strata. Assuming potential patient attrition, it was estimated that about 42 subjects may need to be enrolled initially for each treatment group within each stratum to achieve the desired n of 29 subjects per group within each stratum.

Pre-specified secondary efficacy endpoints and analyses:

1. To determine the proportion of subjects with a PedACR30 response at Week 16.
2. To determine and compare time to onset of flare in non-MTX/adalimumab-treated polyarticular JRA subjects to non-MTX/placebo-treated polyarticular JRA subjects.
3. To determine and compare time to onset of flare in MTX/adalimumab-treated polyarticular JRA subjects to MTX/placebo-treated polyarticular JRA subjects.
4. To determine and compare the proportions of subjects with disease flare by the end of the DB phase (Week 48) for subjects treated in the MTX-stratum (pre-specified analysis: Chi-square test).
5. To determine continued clinical benefit at the 30%, 50%, and 70% improvement response (as documented by the Pediatric ACR 30/50/70 criteria) after repeated SC administration of adalimumab:
i) To determine the proportions of subjects with a PedACR30/50/70 response at the end of the DB phase (Week 48) in all groups and both strata.
ii) To determine the proportions of subjects with PedACR30/50/70 response in the OLE BSA phase in both strata.
5. To compare the efficacy of FD every other week (eow) based on body weight to variable eow dosing based on BSA of subjects rolled over into the OLE phases of the trial (this objective was added in a later protocol amendment) through determination of the proportion of subjects with PedACR30/50/70 response in the OLE-FD phase.

Other efficacy variables:

1. To determine serum adalimumab concentrations.
2. To determine serum levels of anti-adalimumab antibodies.

Safety

Assessment of safety of adalimumab treatment was to be achieved through pre-specified evaluation of serious adverse events, deaths, adverse events, changes in laboratory parameters, physical exams, and vital signs.

Pharmacokinetic objectives:

Primary:

To estimate adalimumab population pharmacokinetic parameters in pediatric subjects (at least 4 years old) with poly-articular JRA.
Secondary:
1. To characterize adalimumab pharmacokinetics and identify important subject characteristics that will explain pharmacokinetic variability in pediatric subjects with polyarticular JRA.
2. To compare adalimumab pharmacokinetics in children with JRA to adult RA subjects.
3. To compare the pharmacokinetics of FD eow based on body weight to variable eow dosing based on BSA of subjects rolled-over into the OLE FD phase of the trial whose pharmacokinetic samples were drawn (added as an amendment).

Populations for analysis:

It was pre-specified that the efficacy and safety analyses were to be performed in 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 following four populations were used to analyze different phases of the study:

1. The OL-LI population includes any ITT subject that received at least one dose of adalimumab in the OL-LI phase of the trial (initial 16 weeks).
2. The DB population includes any ITT subject that received at least one dose of DB medication (32 week period).
3. The OLE-BSA population includes any ITT subject that received at least one dose of adalimumab in the OLE-BSA phase (duration varied from 32 to 136 weeks depending on if the subject flared in the DB phase and when they entered the OLE FD phase).
4. The OLE-FD population includes any ITT subject that received at least one dose of adalimumab at an FD of 20 mg or 40 mg (16 weeks for analysis of efficacy and 48 weeks for analysis of safety).

Conclusions on the study design

Overall, the study design was adequate and provided an opportunity to reasonably assess the benefits of adalimumab treatment alone or in combination with MTX in the target patient population. However, it is important to note that some factors in the study design likely influenced the subsequent results of the study:

1. The extension phases of the study (OLE-BSA and OLE-FD) were conducted on the outcome-enriched population (PedACR $\geq$ 30 responders at the end OL-LI), which maximized the observed response rates.

2. The definition of flare and the ACR pediatric criteria were constructed on the same set of variables and the worsening of the disease called "flare" in the DB phase merely reflected the predefined worsening of the ACR pediatric response from that observed at the end of the OL-LI phase. Additionally, the amendment with modification of the flare definition introduced the possibility to rescue the flaring placebo-treated subjects faster, but also

may have led to an increase in the number of flares resulting in more events counted for the primary endpoint in both strata.

3. All subjects were exposed to adalimumab at the initial OL-LI phase of the study; therefore, the control group of those taking placebo in the DB phase still consisted of the subjects who were exposed to the study drug previously. In the setting of the properly chosen endpoints for the randomized withdrawal design this did not impact the efficacy assessment as much as it was likely to impact the safety assessment. In the given circumstances, the safety assessment was limited since the comparison was not against a "no drug exposure" control group, but against the group currently taking placebo but previously exposed to the study drug (also refer to Section 7.1).

6.1.4 Efficacy Findings

6.1.4.1 Study conduct

Amendments to the protocol and the statistical analysis plan:

Protocol amendments:
Six amendments were made to the final protocol (25 Apr 2002).

1. Amendment 1 (editorial changes/clarifications; 24 Jun 2002).
2. Amendment 2 (an additional pharmacokinetic sample and the OLE were added to the study; 26 Sep 2002).
3. Amendment 3 (expanded the safety assessments to include a serum pregnancy test on all females aged ≥ 10 years at all visits and clarified the visit schedule for the OLE phase; modified the definition of disease flare; 03 Jul 2003).
4. Amendment 4 (extended the OL LI phase and clarified study visits and the requirements for chest radiography- CXRs; 05 Feb 2004).
5. Amendment 5 and Amendment 6 were incorporated to change the study visit schedule to allow for pharmacokinetic sampling and validate safety and efficacy of new FD regimen, to change the evaluation time period for joints injected with intra-articular and/or soft-tissue corticosteroids from non-evaluable for the duration of the study to evaluable after three months, to clarify that the DSMB will not participate in the OLE BSA and OLE FD phases of this trial, to list additional visits at which Tanner Score should be completed, to update the contact information in title page, US contact information for AE reporting, packaging and labeling information, drug return information, Abbott Monitor information; 26 Aug 2005).

Changes in the Statistical Analysis Plan:

i) Disease flare was determined for blinded subjects at DB Baseline.
ii) The disposition of subjects who were PedACR30 responders but did not enroll into the DB phase was analyzed.

iii) The AE overview data was analyzed for the combined OL-LI and DB phases by event per 100/patient years (PYs).
iv) Most frequent (≥ 5%) infectious AEs were analyzed by events per 100 PYs.
v) Summary data for Tanner staging was to be done instead of comparison data.
vi) The inclusion of PedACR90 response criteria.

Patient disposition:

Study DE038 enrolled a total of 171 patients. Tables 3-5 summarize the disposition of patients in study DE038. See Section 7.1.3 for a detailed explanation of the reasons for premature discontinuation of study participation.

Overall, the degree of patient attrition in the study was modest and did not interfere with the interpretation of the study results. The initial 7 % dropout from the OL-LI phase reflected some immediately observed known drug toxicities (cytopenia, pneumonia, LFT abnormalities); one case of unexpected CPK elevation and one case of moderate metrorrhagia. The withdrawals due to lack of efficacy included both lack of response and frank JRA flares while on study treatment. The subsequent 15% dropout prior to randomization into the DB phase primarily reflected lack of response to the study drug, mainly in the monotherapy stratum. In the DB phase, patient attrition was minimal and did not interfere with the results of the primary efficacy endpoint. No dropout due to adverse events was reported by the Sponsor in the DB phase. The largest dropout rate, close to ~20 %, was observed in the OLE-BSA phase which was also the longest phase of the study exceeding 2 years of participation for the majority of patients; even in that phase the main reasons for discontinuations were administrative, such as inability to continue into the OLE-FD phase (Section 7.1.3). Interestingly, a few subjects discontinued study treatment as their JRA went into remission. The rate of dropouts in the OLE-FD phase was comparable with other phases taking into consideration the duration of each phase. No signal of increased dropout with dose increase was seen in the OLE-FD phase. Isolated protocol violations leading to dropouts were seen in each phase of the study and are described in Section 7.1.3. Overall, no protocol violations that would influence the results of the study were observed.

Table 3.

Patient disposition in OL-LI and DB phases of the study.

OL LI phase (16 weeks)	All patients	Non-MTX		MTX	
All randomized patients, n(%)	171 (100)	86 (100)		85	
Completers, n(%)	159* (93)	77(90)		82(96)	
Patients prematurely discontinued before week 16, n(%)	12(7)	9(10)		3(4)	
Adverse event, n(%)	4(2)	2(2)		2(2)	
Lack of efficacy, n(%)	6(4)	6(7)		0	
Withdrawal of consent, n	1	0		1	
Lost to follow up, n	1	1		0	
Patients completed the OL-LI and did not enroll into DB phase, primary reason for not enrolling, n(%)	26(15)	19(22)		7(8)	
Adverse event, n	3	3		0	
Lack of efficacy, n	4	4		0	
Other, n	15	9		6	
Protocol violation, n	2	1		1	
Withdrew consent, n	2	2		0	
DB phase (32 weeks)	All patients	Non-MTX		MTX	
		Adalimumab	Placebo	Adalimumab	Placebo
All randomized patients, n(%)	133(100)	30(100)	28(100)	38(100)	37(100)
Completers, n(%)	128(96)	29(97)	28(100)	35(92)	36 (97)
Patients prematurely discontinued before week 48, n(%)	5	1	0	3	1
Other, n(%)	3	0	0	3	0
Withdrawal of consent, n(%)	1	0	0	0	1
Protocol violation, n(%)	1	1	0	0	0

Source: Sponsor's Table 6, page 205 of clinical study report (CSR); Tables 14_13.1.2 and 14_3.1.3.

*One subject from the MTX stratum (#5302) discontinued study participation after 8 weeks of treatment due to elevated liver function tests (see Section 7.1.3). This subject was not counted by the Sponsor as a study drop out in their original disposition table; the outcome for this subject was re-adjudicated after reviewing the respective clinical research form -CRF.

Table 4.

Patient disposition in the OLE-BSA phase.

OLE-BSA (up to 136 weeks)	All patients	Non-MTX		MTX	
		Adalimumab*	Placebo*	Adalimumab*	Placebo*
All enrolled patients	128(100)	29(100)	28(100)	35(100)	36(100)
Completers, n (%)	106(83)	24(83)	23(82)	31(89)	28(78)
Patients who discontinued before the beginning of OLE-FD phase, n (%)	22(17)	5(17)	5(18)	4(11)	8(23)
Adverse event, n (%)	2	0	1	0	1
Lack of efficacy, n (%)	4	0	1	0	3
Withdrawal of consent, n (%)	9	4	2	1	2
Other, n (%)	6	0	1	2	3
Protocol violation, n(%)	1	1	0	0	0

Source: Sponsor's Table 6, page 205 of clinical study report (CSR); Tables 14_13.1.2 and 14_3.1.3.
*treatment received according to the assignment in the DB phase

Table 5.

Patient disposition in the OLE-FD phase.

OLE-FD (48 weeks)	All patients	Adalimumab					MTX plus adalimumab				
		Incr dose 5mg	Incr dose 10mg	Incr dose > 10mg	Same dose	Decr dose	Incr dose 5 mg	Incr dose 10 mg	Incr dose >10 mg	Same dose	Decr dose
All enrolled patients, n(%)	106 (100)	7	7	8	23	2	18	9	4	27	1
Patients discontinued before week 48, n(%)	10(9)	5(23%)			2(8%)		0			3(11%)	
Adverse event, n	3	0			1		0			2	
Other, n	3	2			1		0			0	
Lost to follow up, n	2	2			0		0			0	
Withdrew consent	1	0			0		0			1	
Protocol violation	1	1			0		0			0	

Source Table: 2.1_3; 120-day safety update

Demographic characteristics of the study participants:

OL-LI phase: The demographic characteristics of the study participants at the baseline of the OL-LI phase are shown in Table 6. Note: The Sponsor collected all the information defined in the statistical analysis plane (SAP); only relevant characteristics are presented in the Tables 6-8.

The study sample consisted primarily of white (92%) females (79%) with the mean weight of 42 kg and mean height of 144 cm. Approximately 40% of the subjects were in the oldest group (13-17 years), ~23% were in the youngest group (4-8 years). Overall, the demographic characteristics were similar between the two strata and reflected the characteristics of the target JRA population.

Table 6. Demographic characteristics of the study participants at the baseline of OL-LI phase.

Demographic characteristic	MTX stratum N=85	Non-MTX stratum N=86	Overall N=171
Age Mean(SD)	11(3)	11(4)	11(4)
Age group (n, %)			
4-8 years	19(22)	21(24)	40(23)
9-12	30(35)	32(37)	62(36)
13-17	36(42)	33(38)	69(40)
Gender (n, %)			
Female	68(80)	67(78)	135(79)
Race			
White	82(95)	76(88)	157(92)
Black	0	3(4)	3(2)
Asian	0	2(2)	2(1)
American Indian/ Alaskan Native	1(1)	1(1)	2(1)
Unknown	2(2)	4(5)	6(4)
Other	1(2)	0	1(<1)
Body weight, kg, Mean(SD)	44(18)	41(19)	42(19)
BMI, kg/m^2 Mean(SD)	20(5)	19(5)	19(5)
Height, cm, Mean(SD)	145(19)	144(20)	144(20)
Tanner stage, n (%)			
1	29(34)	38(44)	67(39)
2	21(25)	12(14)	33(19)
3	5(6)	5(6)	10(6)
4	12(14)	17(20)	29(17)
5	18(21)	14(16)	32(19)

Adopted from Sponsor's Table 13, p. 217 CSR

DB phase: The demographic characteristics of subjects treated with adalimumab or placebo within the non-MTX stratum were similar and allowed comparison of treatment effects within

this stratum. Fewer subjects were in the non-MTX stratum (n=58) compared to the MTX stratum (n=75) due to patient attrition for lack of efficacy in the monotherapy stratum after the OL-LI phase. The demographic characteristics of the two groups in the MTX stratum were similar except for the unequal distribution of the youngest children (age 4-8 years), between the two arms; twice as many children were treated with placebo (n=12, 32%) compared with the active treatment group (n=6, 16%). This imbalance possibly occurred due to random chance likely related the small number of children.

Table 7. Demographic characteristics for the participants of the DB phase.

Demographic characteristic	MTX stratum N=75		Non-MTX stratum N=58	
	Placebo N=37	Adalimumab N=38	Placebo N=28	Adalimumab N=30
Age Mean(SD)	11(3)	12(3)	11(4)	11(4)
Age group (n, %)				
4-8 years	12(32)	6(16)	8 (29)	8(27)
9-12	10(27)	17(45)	7(25)	10(33)
13-17	15(41)	15(39)	13(46)	12(40)
Gender (n, %)				
Female	30 (81)	30(79)	20(71)	23(77)
Race				
White	36(97)	36(95)	27(96)	26(87)
Black	0	0	1(4)	1(3)
Asian	0	0	0	1(3)
American Indian/ Alaskan Native	1(3)	0	0	1(3)
Unknown	0	1(3)	0	1(3)
Other	0	1(3)	0	0
Body weight, kg, Mean(SD)	44(19)	42(18)	45(24)	41(17)
BMI, kg/m^2 Mean(SD)	21(5)	19(5)	19(6)	19(5)
Height, cm, Mean(SD)	143(23)	145(16)	148(21)	144(20)
Tanner stage, n (%)				
1	14(38)	12(32)	9(32)	12(40)
2	7(19)	9(24)	5(18)	2(7)
3	2(5)	5(13)	1(3)	4(13)
4	7(19)	6(16)	6(21)	7(23)
5	7(19)	6(16)	7(25)	5(17)

Adopted from Table 14, p 219 CSR
The dose of adalimumab was 24 mg/m2, BSA eow

OLE-BSA phase: In the OLE-BSA phase, there was a similar distribution of the demographic characteristics for the participants (n=128) between the strata and between the groups within each stratum by previous assignment from the DB phase (data not shown).

OLE FD phase: One hundred and six subjects participated in the OLE-FD phase. Table 8 shows the demographic characteristics of the participants of the OLE-FD phase. When comparing the OL-LI baseline characteristics of the children who had their dose increased to those who had their dose unchanged or decreased upon entering the OLE-FD phase, the children from the increased dose group were primarily younger children (n=20 [38%] vs n=10 [19%] in the 4-8 years age group and n=23[43%] vs n=9[17%] in the 9-12 years age group) whose maturation level was still in Tanner stage 1 (n=31, 58%). Further, children who had their dose increased were smaller (mean weight 33 kg, mean height 135 cm) than the children whose dose was either decreased or left unchanged (mean weight 54 kg, mean height 153 cm). See further discussion in Section 8.1.

Table 8. Demographic characteristics of children participating in the OLE-FD phase.

Demographic characteristics	MTX stratum		Non-MTX stratum		Overall	
	Same/ Decreased dose N=28	Increased dose N=31	Same/ Decreased dose N=25	Increased dose N=22	Same/ Decreased dose N=53	Increased dose N=53
Age Mean(SD)	12(3)	10(3)	12(4)	10(4)	12(4)	10(3)
Age group, years (n, %)						
4-8	4(14)	11(36)	6(24)	9(41)	10(19)	20(38)
9-12	5(18)	15(48)	4(16)	8(36)	9(17)	23(43)
13-17	19(68)	5(16)	15(60)	5(23)	34(64)	10(19)
Gender (n, %)						
Female	20(71)	28(80)	17(68)	16(73)	37(70)	41(77)
Race						
White	26(92)	30(97)	22(88)	21(96)	48(90)	51(96)
Black	0	0	1(4)	0	1(2)	0
Asian	0	0	1(4)	0	1(2)	0
American Indian/ Alaskan Native	0	1(3)	1(4)	0	1(2)	1(2)
Unknown	1(4)	0	0	0	1(2)	0
Other	1(4)	0	0	1(4)	1(2)	1 (2)
Body weight, kg, Mean(SD)	55(18)	33(11)	52(54)*	33 (10)	54(21)	33(11)
BMI, kg/m^2 Mean(SD)	22(5)	18(5)	21(6)	17(3)	22(6)	18(4)
Height, cm, Mean(SD)	155(20)	134(16)	151(24)	136(14)	153(22)	135(15)
Tanner stage, n (%)						
1	5(18)	17(55)	7(28)	14(64)	12(23)	31(58)
2	4(14)	10(32)	2(8)	2(9)	6(11)	12(23)
3	3(11)	1(3)	1(4)	1(4)	4(8)	2(4)
4	7(25)	2(6)	7(28)	3(14)	14(26)	5(9)
5	9(32)	1(3)	8(32)	2(9)	17(32)	3(6)

Adopted from Table 16, p.225, CSR.
*median (range) weight in kg for this group: 55(16-99)

Baseline patient disease characteristics

The Sponsor presented data on the majority of the pre-specified patient disease characteristics, except three variables that were not included in the original sBLA submission: morning stiffness, patient's global assessment, and anti-dsDNA antibodies. An information request was sent to the Sponsor during the review process and the Sponsor responded that the data were not collected for patients' global and morning stiffness due to poor reliability of these parameters in the given patient population (this change was indicated in the first protocol amendment); the data on anti-dsDNA antibodies were subsequently submitted by the Sponsor on October 31, 2007 in their response to the Agency's information request and included in Section 7.1.3.

OL-LI phase: Table 9 below shows the baseline patient-disease characteristics for subjects who participated in the OL-LI phase. The mean tender, swollen, and active joint counts were 10, 13, and 15 in the MTX stratum and 13, 16, and 19 in the non-MTX stratum, respectively, reflecting the moderate to severe disease that was slightly better controlled at baseline in the MTX stratum. Other characteristics such as childhood health assessment questionnaire (DICHAQ) scores and joints with limitation of motion (LOM) also appeared better controlled in the subjects treated with MTX. These differences in the baseline patient-disease characteristics may be related to the clinical effect of MTX treatment. These differences do not raise concerns about interpretation of the study since the study was designed and conducted in two strata with the understanding that the baseline patient-disease characteristics and the overall efficacy and safety results may be different with the combination treatment (adalimumab and MTX) compared to adalimumab monotherapy.

Of note, the previous disease modifying anti-rheumatic drugs (DMARDs) used in this population included methotrexate, hydroxychloroquine, sulfasalazine, and cyclosporine (Sponsor's Table 14.1_8.1).

Table 9. Baseline patent-disease characteristics for subjects participating in the OL-LI phase.

Baseline patient-disease characteristics*	MTX N=85*	Non-MTX N=86*
Duration of JRA Median (range) years	3(0-16)	2(0-14)
RF+, n (%)	19(23)	18(21)
Tender joint count (75 joints), mean (SD)	10 (10)	13 (14)
Swollen joint count (66 joints), mean (SD)	13(7)	16(11)
Pain on passive motion joint count (75 joints), mean(SD)	8(7)	13(14)
Limitation of passive motion joint count, mean (SD)	13(8)	14(10)
Active joint count, mean (SD)	15(8)	19(12)
CRP, Abnormal, n(%)	51(61)	61(71)
DICHAQ, Mean (SD)	0.9(0.6)	1.2(0.8)
Physician's global assessment of disease activity; VAS, 0-100 mm, Mean (SD)	58 (17)	60 (19)
Parent's global assessment of disease activity; VAS, 0-100 mm, mean (SD)	43(22)	53(23)
Previous, other than MTX, DMARDs use, n(%)		
0	66(78)	61(71)
1	16(19)	24(28)
2	3(4)	1(1)
MTX dose, mg, median (range)	15(2.5-36)	0

Data adopted from Table 17, p. 228, CSR.
* The N varied by 1-2 for some of the variables due to differences in data availability.

DB phase: Table 10 shows the patient-disease characteristics for the subjects participating in the DB phase. The same trend as was observed in the OL-LI phase was observed in the DB phase where more active disease is seen in the non-MTX stratum. The patient-disease characteristics appear to be generally similar between the groups within each stratum.

Table 10. Patient-disease characteristics for the subjects participating in the DB phase.

Baseline disease characteristics	MTX N=75**		Non-MTX N=58**	
	Placebo N=37	Adalimumab N=38	Placebo N=28	Adalimumab N=30
Duration of JRA, Median (range), years	3(0-16)	2(0-16)	1(0-13)	2(0-14)
RF+, n (%)	6(17)	10 (27)	6(22)	6(20)
Tender joint count (75 joints), mean (SD)	9(10)	12(11)	15(17)	13(13)
Swollen joint count (66 joints), mean (SD)	14(7)	14(8)	17(12)	15(10)
Pain on passive motion joint count (75 joints), mean(SD)	7(7)	9(8)	11(14)	11(12)
Limitation of passive motion joint count, mean (SD)	11(7)	14(10)	15(12)	13(9)
Active joint count, mean (SD)	15(8)	15(8)	20(13)	19(11)
CRP, Abnormal, n(%)	20(56)	24 (63)	21(75)	18(60)
DICHAQ, Mean (SD)	0.9 (0.6)	1.0(0.6)	1.3(0.7)	1.1(0.7)
Physician's global assessment of disease activity; VAS, 0-100 mm, Mean (SD)	60(16)	56(18)	60(19)	60(18)
Parent's global assessment of disease activity; VAS, 0-100 mm, mean (SD)	41(24)	46(19)	57(21)	53(26)
Previous, other than MTX, DMARDs use, n(%)				
0	26(70)	30(79)	21(75)	19(63)
1	9(24)	7(18)	7(25)	10 (33)
2	2(5)	1(3)	0	1(3)
MTX dose, mg, median (range)	15 (6-25)	15 (2.5-30)	0	0

The baseline patient-disease characteristics on the basis of pre-treatment prior to OL-LI phase.
** The N varied by 1-2 for some of the variables due to differences in data availability.
Adopted from the Sponsor's Table 18, p 230, CSR

OLE-BSE phase: A similar distribution of patient-disease characteristics was observed in subjects participating in the OLE-BSA phase as in the earlier phases (data not shown).

OLE-FD phase: In the OLE-FD phase, apart from the previously observed difference between the MTX and non-MTX strata, children who had their dose increased were primarily rheumatoid factor negative (RF-) at baseline (Table 11).

Table 11. Patient-disease characteristics in subjects who participated in the OLE-FD phase.

Baseline disease characteristics	MTX N=59		Non-MTX N=57	
	Same/ Decreased dose N=28*	Increased dose N=31*	Same/ Decreased dose N=25*	Increased dose N=22*
Duration of JRA, Median (range), years	3(0-12)	4(0-12)	2(0-14)	2(0-14)
RF+, n (%)	11(41)	2(7)	10 (40)	0
Tender joint count (75 joints), mean (SD)	10(10)	12(11)	14(12)	14(14)
Swollen joint count (66 joints), mean (SD)	13(7)	12(7)	17(10)	15(12)
Pain on passive motion joint count (75 joints), mean(SD)	6(5)	10(8)	13(12)	8(8)
Limitation of passive motion joint count, mean (SD)	11(7)	14(10)	16(9)	13(10)
Active joint count, mean (SD)	15(6)	14(9)	19(11)	18(13)
CRP, Abnormal, n(%)	13(46)	22(73)	18(72)	14(64)
DICHAQ, Mean (SD)	0.8(0.6)	1(0.6)	1.2(0.8)	1.2(0.7)
Physician's global assessment of disease activity; VAS, 0-100 mm, Mean (SD)	59(15)	56(17)	58(20)	63(17)
Parent's global assessment of disease activity; VAS, 0-100 mm, mean (SD)	42(20)	42(23)	56(23)	53(21)
Previous DMARD use, n(%)				
Yes	5(18)	5(16)	5(20)	7(32)

Data from Sponsor's Table 20, p 238, CSR.
* The N varied by 1-2 for some of the variables due to differences in data availability

Other baseline characteristics:

A few subjects from each stratum used tobacco (MTX – 3/85 subjects; non-MTX – 3/86 subjects) or alcohol (MTX– 2/85 subjects; non-MTX – 3/86 subjects) prior to study participation. PPD skin test was performed in 64 subjects in MTX stratum (positive in 2/64 subjects) and in 75 subjects in non-MTX stratum (positive in 1/75 subjects). According to the study protocol, chest radiographs were scheduled to be done at the time of screening only and were required for all subjects who were PPD-positive. From the MTX stratum 36/85 subjects had chest radiographs; two were found abnormal. From the non-MTX stratum, 29/86 subjects had chest radiographs, 4 were found abnormal.

The Division requested an explanation from the Sponsor about the time course of study subjects who (1) were PPD-positive and (2) had abnormal chest radiographs. The Sponsor provided the explanation in their subsequent response to the information request submitted on July 31, 2007.

The three subjects who were found PPD positive all had normal chest radiographs. One of the subjects discontinued during the OLE-BSA phase on day 564 because of a reported remission;

two other subjects are ongoing in the study. None of the subjects experienced TB infection or any serious adverse events.

Table 12 shows the abnormalities in CXR and the outcomes for the subjects whose CXRs were found abnormal at study entry. As shown, none of the subjects had evidence of TB infection; only 1 subject later developed a serious pulmonary adverse event – pneumonia.

Table 12. Subjects with abnormalities on chest radiographs upon study entry.

Subject #	Gender/age	CXR reading	Status in the study	Pulmonary AEs experienced during or after drug exposure
9202	F/16	Pulmonary fibrosis (likely due to MTX toxicity)	Discontinued from OL-LI on day 42 for metrorrhagia;	Pneumonia on day 56
5403	F/14	Scoliosis	Ongoing	Chronic bronchitis, URI, viral URI
4104	F/7	Bilateral interstitial pneumonitis	Ongoing	Rhinitis, tracheobrochitis, nasopharyngitis, sinusitis, URIs
4105	F/11	Emphysema	Ongoing	Acute tonsillitis X 3
1704	F/17	Pleural scarring (likely due to previous h/o pleuritis)	Ongoing	Not reported
7204	F/12	Prominent hilar vascular structure	Discontinued from OL-LI on day 85	Not reported

6.1.4.2 Analysis of efficacy

The efficacy review is focused primarily around the analysis of the onset of action of adalimumab in the OL-LI phase of the study, comparison of the continued adalimumab treatment with placebo treatment in the DB randomized withdrawal phase of the study, analysis of maintenance of the observed response in the OLE-BSA phase of the study and further maintenance of response upon switching to the treatment with the fixed dosing regimen in the OLE-FD phase of the study.

OL-LI phase: At the end of the 16 week period of open label treatment with adalimumab alone or in combination with MTX, the following PedACR 30 response rates were observed in the ITT population (n=171):

- MTX stratum – 80/85 (94%) subjects were PedACR 30 responders;
- Non-MTX stratum – 64/86 (74%) subjects were PedACR 30 responders.

Subsequent analysis of the onset of action of the study treatment demonstrated that the PedACR 30 response appeared after two weeks of treatment in more than one half of patients in both strata (54% in the MTX stratum and 66% in the non-MTX stratum). It appeared that more

subjects in the non-MTX stratum initially experienced PedACR responses in all categories compared to MTX stratum (at the 2 week time point). The response rates became similar in both strata at week 4 and then increased only slightly in the non-MTX stratum but continued to increase steadily in the MTX stratum reaching higher response rates with the combination therapy (Table 13).

Table 13. PedACR response rates at different time points in the OL-LI phase.

	MTX + adalimumab N=85				Adalimumab N=86			
Time points	PedACR 30	PedACR 50	PedACR 70	Ped ACR 90	Ped ACR 30	Ped ACR 50	PedACR 70	Ped ACR 90
Week 2	46 (54)	24(28)	7(8)	1(1)	57 (66)	36 (42)	14(16)	1(1)
Week 4	63 (74)	41(48)	18(21)	2(2)	63 (77)	45 (52)	22(26)	3(4)
Week 8	74 (87)	64(75)	38(45)	7(8)	60 (70)	47 (55)	28(33)	6(7)
Week 12	75 (88)	71(84)	46(54)	21(25)	67 (78)	59 (69)	39(45)	10(12)
Week 16	80 (94)	77(91)	60(71)	24(28)	64 (74)	55 (64)	40(46)	22(26)

Because the PedACR response is a composite score consisting of six variables, it was important to understand whether there were any variables or aspects of JRA that particularly changed or did not change with the administered treatment. Table 14 demonstrates changes in each of the JRA core set criteria in the study participants.

Table 14. Mean percent changes (and mean absolute changes for CRP) from baseline in JRA core variables.

	Physician Global		Parent Global		N active joints	
	MTX	Non-MTX	MTX	Non-MTX	MTX	Non-MTX
Baseline (VAS, 0-100)	58	60	43	53	15	19
% change at Week 4	-49	-44	1	-40	-40	-40
% change at Week 8	-61	-46	-33	-42	-60	-46
% change at Week 12	-63	-58	-34	-34	-64	-50
% change at Week 16	-71	-64	-59	-49	-71	-56

	N joints with LOM		CRP (mg/dl)*		CHAQ	
	MTX	Non-MTX	MTX	Non-MTX	MTX	Non-MTX
Baseline	13	14	2.3	2.9	0.9	1.2
% change at Week 4	-35	-32	178 (-1.4)	-28 (-1.5)	-34	-36
% change at Week 8	-53	-39	20 (-1.6)	10 (-1.1)	-46	-37
% change at Week 12	-59	-43	-10 (-1.5)	42 (-1.7)	-63	-34
% change at Week 16	-65	-44	25 (-1.8)	-24 (-1.6)	-64	-34

* values indicated in the parentheses are mean changes in CRP in mg/dl per group

As can be seen from the Table 14, both subjectively reported and objectively observed variables improved in both strata with adalimumab treatment. The improvements were seen in all aspects of JRA covered by the composite score of PedACR response criteria and did not seem to be driven by selected variables. Of note, mean CRP values overall improved, however there were several subjects in both strata who developed JRA flares; these subjects' CRP values increased during the flares and inconsistently pulled the group means toward the higher range.

DB phase: All subjects enrolled in the DB phase (n=133) were PedACR 30 responders after the OL-LI phase. All subjects were randomized into placebo and adalimumab groups within their original stratum. The duration of treatment was 32 weeks. The following four treatment regimens were administered to the study participants:

- placebo every other week subcutaneously,
- adalimumab 24 mg/m^2 every other week subcutaneously,
- stable dose of MTX and placebo every other week subcutaneously,
- stable dose of MTX and adalimumab 24 mg/m^2 every other week subcutaneously.

Primary efficacy endpoint:

The primary efficacy endpoint was a comparison of the proportions of subjects with disease flares between the adalimumab and the placebo groups within the non-MTX stratum. The Chi-square test was used for the comparison of proportions. The sample size of 29 subjects per group within each stratum was originally calculated based on the assumption of 40% difference in the flare rates. All dropouts and subjects with missing data were treated as non-responders, regardless of the reasons for missing data (imputation method #1 used for primary efficacy analysis).

The observed efficacy of adalimumab treatment is shown in Table 15. Adalimumab alone at dose 24 mg/m^2 was superior to placebo in maintaining the clinical benefit reflected by difference in disease flares in PedACR 30 responder enriched population of children with polyarticular JRA. Fewer subjects treated with adalimumab had JRA flares compared to subjects treated with placebo.

Table 15. Proportion of subjects with flares in the DB phase.

Stratum	Placebo	Adalimumab	p-value
Non-MTX	**20/28 (71%)**	**13/30 (43%)**	**0.031**
MTX	24/37 (65%)	14/38 (37%)	0.015

Bold red shows the results of the pre-specified primary efficacy analysis with Chi-square test

Two pre-specified sensitivity analyses with different imputation methods were used by the Sponsor to further assess the results of the primary efficacy analysis (non-MTX stratum):

1. Subjects with missing values were treated as non-responders (having a disease flare) except for the placebo-treated subjects who reported a primary reason for drop out other than disease flare (pre-specified imputation method #2). However, no subjects in the placebo group of non-MTX stratum withdrew for reasons other than disease flare (see Table 3). The results of this analysis using the imputation method # 2 were identical to the results of the primary analysis.

2. Last Observation Carried Forward (LOCF) was the pre-specified imputation method #3. Subjects with missing values had their responses imputed with LOCF which resulted in a decrease by 4 from the number of subjects with flares in the adalimumab group and in a decrease by 1 from the number of subjects with flares in the placebo group. This resulted in a smaller numerator in the adalimumab group (9/30-30%) and almost the same numerator in the placebo group (19/28-68%) leading to a p-value numerically smaller than the p-value of the primary analysis (p= 0.004).

Thus, the pre-specified primary efficacy analysis demonstrated statistically significant superiority of adalimumab monotherapy over placebo in maintenance of clinical benefit in PedACR 30 enriched population with poly-articular JRA. The two pre-specified imputation methods supported the results of the primary efficacy analysis.

To further explore the effects of adalimumab treatment on different aspects of JRA and investigate which of the core JRA variables changed with appearance of flares, mean changes in each of the JRA core variables in subjects who flared in the DB portion of the study were examined (Table 16). The data suggest that all of the variables comprising the flare definition worsened with occurrence of flares. More pronounced worsening was observed in the placebo-treated groups. Subjects treated with adalimumab monotherapy appeared to have slightly more worsening in the physician and parent global assessments and more active joints compared to subjects treated with placebo, although the interpretation is limited to the analysis of mean changes. Importantly, the degree of worsening was modest and did not reach the disease activity recorded at the baseline of the OL-LI phase, likely owing to the pre-specified flare definition (Section 6.1.3).

Table 16. Mean changes in the core JRA variables from DB baseline to DB final visit in subjects who flared.

Treatment	PhGA (0-100)	PGA (0-100)	N of joints with LOM	N of active joints	DICHAQ	CRP mg/dl
MTX	23	16	3	4	0.2	3.4
MTX+adalimumab	18	16	2	3	0.3	1.5
Placebo	20	20	5	4	0.3	0.66
Adalimumab	22	34	0.8	7	0.3	0.04

Data from Sponsor's response to IR from July 31, 2007, Tables 11, 12.

To evaluate possible influences of demographic characteristics on the results of the primary efficacy analysis, subgroup analysis was performed and is shown for the non-MTX stratum in Table 17 and for the MTX stratum in Table 18.

The subgroup analysis compares the proportions of responders within each subgroup between the two groups in each stratum. In each subgroup, more subjects treated with placebo developed JRA flares compared to subjects treated with adalimumab, further supporting the results of the primary efficacy analysis and the analysis of flare rates in the MTX stratum. The imbalances in subjects with obesity in the non-MTX stratum and among subjects with recent onset JRA (<1year) are likely randomly occurring phenomena observed owing to the extremely small numbers of subjects.

Table 17. Pre-specified subgroup analysis of flare rates by selected demographic and baseline disease characteristics for the primary efficacy analysis in the non-MTX stratum.

Subsets by demographic characteristics	Placebo (n=28) N(%)	Adalimumab (n=30) N(%)
Age group (n, %)		
4-8 years (n=16)	6/8(75)	2/8(25)
9-12 years (n=17)	6/7(86)	5/10(50)
13-17 years (n=25)	8/13(62)	6/12(50)
Gender (n, %)		
Females (n=43)	14/20(70)	11/23(48)
Males(n=15)	6/8(75)	2/7(29)
Race		
White(n=53)	19/27 (70)	11/26(42)
Non-white (n=5)	1/1(100)	2/3(67)
Duration of JIA, years		
<=1 (n=22)	6/13(46)	3/9(33)
>1 - <=2 (n=8)	2/2(100)	2/6(33)
>2 - <=4(n=12)	4/5(80)	4/7(57)
>4 - <=8(n=10)	6/6(100)	2/4(50)
>8(n=6)	2/2(100)	2/4(50)
CRP		
Normal (n=19)	4/7(53)	5/12(42)
Abnormal(n=39)	16/21(76)	8/18(44)
Body weight, kg		
<40 kg(n=27)	12/14(86)	4/13(31)
>=40kg (n=31)	8/14(57)	9/17(53)
BMI, kg/m^2		
BMI <25- normal(n=48)	15/22(68)	10/26(38)
BM I>=25 - <30 overweight(n=6)	3/3(100)	2/3(67)
BMI >=30 obese(n=4)	2/3(67)	1/1(100)
Tender joint count =0 (n=37)	11/37 (30)	10/37 (27)
Tender joint count >0 (n=21)	9/21(43)	3/21(14)

Source Tables 14.2_2.1, CSR

Table 18. Pre-specified subgroup analysis of flare rates by selected demographic and baseline disease characteristics for the primary efficacy analysis in the MTX stratum.

Subsets by demographic characteristics	Placebo (n=28)	Adalimumab (n=30)
Age		
Age group (n, %)		
4-8 years (n=18)	7/12 (58)	2/6 (33)
9-12 years (n=27)	8/10 (80)	6/17 (35)
13-17 years (n=30)	9/15 (60)	6/15 (40)
Gender (n, %)		
Females (n=60)	19/30 (63)	12/30 (40)
Males(n=15)	5/7 (71)	2/8 (25)
Race		
White(n=72)	23/36 (64)	12/36 (33)
Non-white(n=2)	1/1(100)	0/1
Duration of JRA, years		
<=1 (n=15)	2/7 (29)	3/8 (38)
>1 - <=2 (n=15)	6/8 (75)	0/7 (0)
>2 - <=4(n=14)	3/5 (60)	3/9 (33)
>4 - <=8(n=18)	9/12 (75)	2/6 (33)
>8(n=13)	4/5 (80)	6/8 (75)
CRP		
Normal (n=30)	8/16(50)	5/14(36)
Abnormal(n=44)	14/20(70)	9/24(38)
Body weight, kg		
<40 kg(n=35)	12/17 (71)	7/18 (39)
>=40kg (n=40)	12/20 (60)	7/20 (35)
BMI, kg/m^2		
BMI <25- normal(n=61)	19/28 (68)	11/33 (33)
BMI>=25 - <30 overweight(n=11)	5/7 (71)	2/4 (50)
BMI >=30 obese(n=3)	0/2	1/1 (100)

Source Tables 14.2_2.1, CSR

Influences of prior use of NSAIDs and corticosteroids on the occurrence of disease flares in both non-MTX and MTX strata were investigated by the Sponsor through construction of tri-variable logistic regression model for each stratum. Although limited by a technical discrepancy between the number of subjects and the number of variables included in the model, the logistic regression model showed that the prior use of NSAIDs and corticosteroids did not change the statistically significant association between adalimumab treatment and the rate of the observed JRA flares in either stratum (data not shown).

Secondary efficacy endpoints:

1) Efficacy of study treatment in the MTX stratum.

To evaluate the effects of the combination therapy of adalimumab and MTX compared with MTX alone, an analysis within the MTX stratum was performed and is shown in Table 15. The treatment with the combination of adalimumab and MTX was statistically superior compared to treatment with MTX alone. The imputation methods #2 (23/37 [62%] vs 14/38 [37%], p=0.028) and #3 (20/37 [54%] vs 8/38[21%] p=0.003) demonstrated results consistent with the pre-specified efficacy analysis within the MTX stratum.

2) Time to disease flare in MTX and non-MTX strata.

To further evaluate clinical benefits of adalimumab treatment, an analysis of time to onset of disease flare from DB baseline was conducted in both strata (Figure 2 and Figure 3).

In the non-MTX stratum, the median time to disease flare from the first dose of DB treatment was approximately 14 weeks for the placebo group, and the median time to disease flare exceeded the 32 week duration of the DB phase for the adalimumab group (log rank test p=0.029). In the MTX stratum, the median time to disease flare was approximately 20 weeks for the placebo group and again exceeded 32 weeks of observation for the adalimumab group (log rank test p=0.031).

Figure 2. Kaplan-Meier curve of time to disease flare, ITT population, DB phase, non-MTX stratum

Adopted from Sponsor's Figure 2, p 267, CSR.

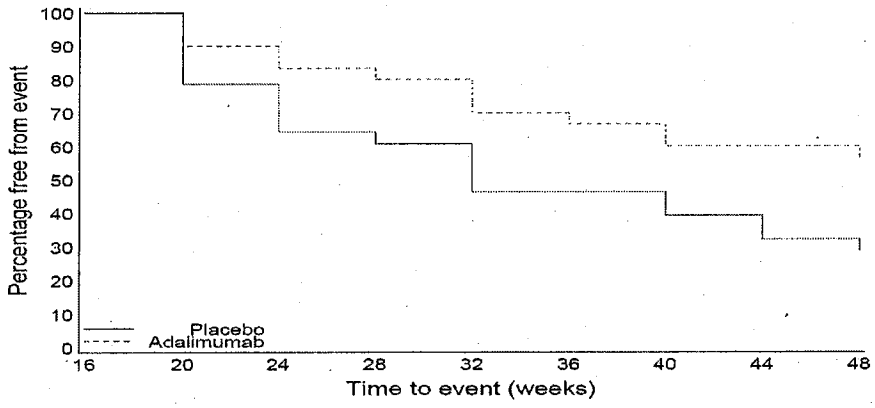
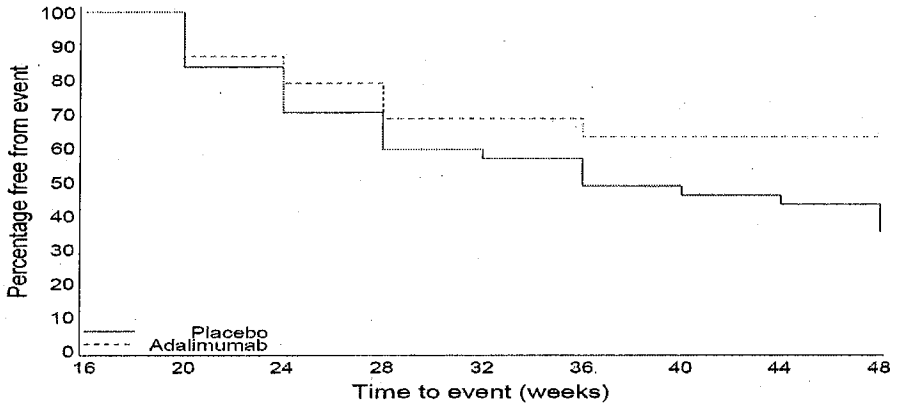


Figure 3. Kaplan Meier curve of time to disease flare, ITT population, DB phase, MTX stratum.
Adopted from Sponsor's Figure 3, p 270, CSR.



This analysis further demonstrates the superiority of adalimumab treatment administered as monotherapy or in combination with MTX in maintenance of PedACR 30 response over placebo (non-MTX stratum) or MTX alone (MTX stratum) treatment in patients with polyarticular JRA.

3) Analysis of changes in each JRA core set components among subjects who responded to adalimumab and did not flare in the DB phase.

To further explore the effect of adalimumab treatment on each of the JRA core set components in children who did not flare in the DB phase, an analysis of mean changes in each of the criteria was performed from baseline OL-LI to the end of DB phase (Table 19). This analysis represents exploration of effects of adalimumab treatment in children whose arthritis improved in the OL-LI phase and whose response to treatment was maintained throughout the 48 week period.

Table 19. Mean changes in the JRA core set criteria in subjects who responded to treatment in the OL-LI phase and did not flare during the DB phase.

	PhGA Disease Activity	PGA of Disease Activity	LOM	Number of Active Joints	DICHQ	CRP
MTX stratum						
Placebo (n=15)						
OL Baseline	52	34	10	15	0.67	1.17
DB Baseline	12	15	3	3	0.15	1.11*
Week 48	13	7	3	3	0.11	1.07
Change at Week 48	-39	-27	-7	-12	-0.56	-0.10
Adalimumab (n=24)						
OL Baseline	56	44	15	15	0.86	2.19
DB Baseline	16	11**	4	4	0.23	0.48
Week 48	7	8	3	1	0.10	0.48
Change at Week 48	-49	-36	-12	-14	-0.76	-1.71
Non-MTX stratum						
Placebo (n=9)						
OL Baseline	70	59	9	14	1.44	4.29
DB Baseline	13	21	2	6	0.22	1.38
Week 48	10	9	3	4	0.11	0.38
Change at Week 48	-39	-51	-6	-10	-1.33	-3.91
Adalimumab (n=17)						
OL baseline	57	51	15	19	1.07	2.05
DB Baseline	13	17	9	6	0.43	0.42
Week 48	5	9	5	4	0.34	0.25
Change at Week 48	-52	-42	-10	-15	-0.73	-1.79

* n=14, **n=23
Data from Sponsor's Tables 43 and 44, CSR.

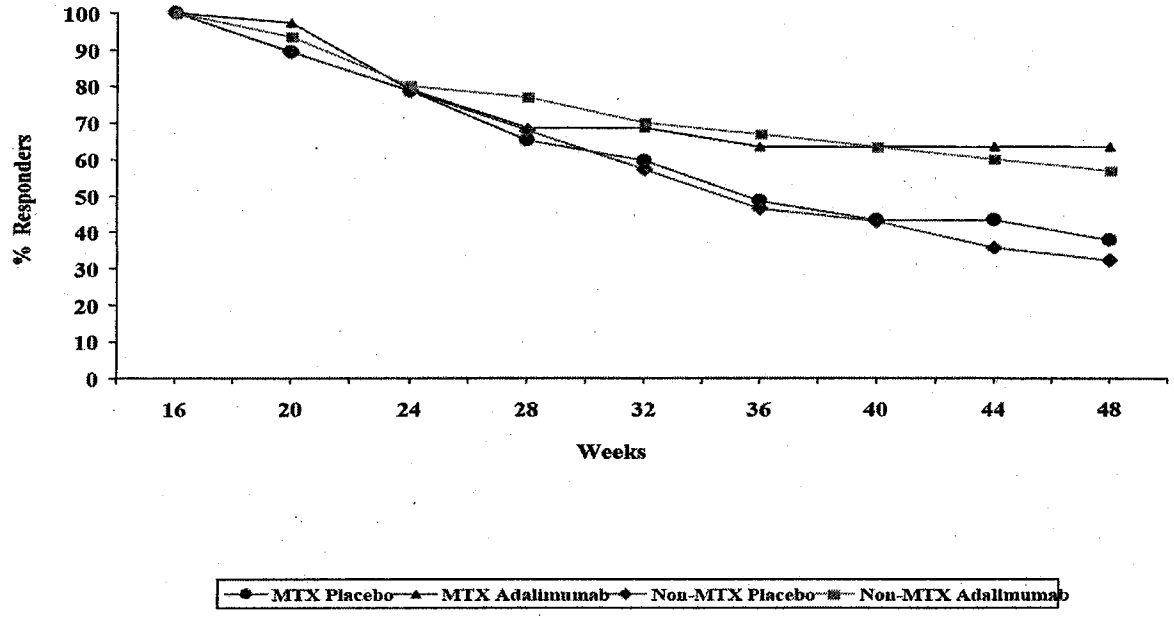
Table 19 shows that substantial improvement occurred in all JRA core set criteria in those children who were able to respond and maintain their responses throughout 48 weeks of treatment in both strata.

4) Analysis of PedACR responses in the DB phase.

PedACR 30 response:

Figure 4 and Table 20 show the PedACR 30/50/70/90 responses during the DB phase. Of note, in this phase, patients who flared or dropped out of the study before week 48 visit for any reason were imputed as PedACR non-responders.

Figure 4. Decline in PedACR 30 response during the DB phase of the study.



Adopted from Sponsor's Figure 4, CSR

All subjects were PedACR 30 responders at the beginning of the DB phase. In the non-MTX stratum, at week 48, 9/28 (32%) subjects receiving placebo and 17/30 (57%) subjects receiving adalimumab remained PedACR 30 resoponders and did not experience worsening of their disease that could meet the pre-specified criteria for JRA flare. In the MTX stratum, 14/37 (38%) subjects receiving placebo and 24/38(63%) subjects receiving adalimumab remained flare-free PedACR 30 responders. The difference between placebo and adalimumab treatment reached nominal statistical significance in the MTX stratum (p=0.028) but not in the non-MTX stratum (p=0.061).

PedACR 50, 70, 90 responses:

Table 20 shows proportions of PedACR 50, 70, and 90 responders among the PedACR 30 responder-enriched population enrolled in the DB phase.

Table 20. Pediatric ACR 50, 70, and 90 response rates.

	Non-MTX stratum		MTX stratum	
	Placebo (n=28)	Adalimumab (n=30)	Placebo (n=37)	Adalimumab (n=38)
PedACR 50 responders				
DB phase Baseline (week 16)	26 (93%)	25 (83%)	35 (95%)	37 (97%)
DB end of phase (week 48)	9(32%)	16(53%)	14(38%)	24(63%)
PedACR 70 responders				
DB phase Baseline (week 16)	20 (71%)	18 (60%)	28 (76%)	27 (71%)
DB end of phase (week 48)	8(29%)	14(47%)	10(27%)	24(63%)
PedACR 90				
DB phase Baseline (week 16)	10 (36%)	12 (40%)	10 (27%)	13 (34%)
DB end of phase (week 48)	5(18%)	9(30%)	10(27%)	16(42%)

Overall, some decline in response was observed with both continuation and withdrawal of adalimumab treatment; not surprisingly, the decrease in responses was more pronounced in the withdrawal groups (placebo and MTX alone) compared to the groups where treatment with adalimumab was continued. Because all subjects who flared in the DB phase were counted as PedACR non-responders according to the pre-specified analysis, the response rates observed in the Table 20 reflect the proportions of subjects whose disease did not worsen to meet the pre-specified flare definition and whose PedACR responses were maintained from the beginning to the end of the DB phase.

OLE-BSA phase: To evaluate the continued benefit of treatment with adalimumab or the combination of adalimumab and MTX in the JRA population, the subjects were further enrolled in the OLE-BSA phase (n=128). The endpoints for the OLE-BSA phase were the PedACR 30/50/70/90 response rates. It is worth noting again that the flare definition in this study was based on the same JRA core set criteria as PedACR response composite scores and merely reflected some predefined clinical worsening of each particular subject's PedACR response. Therefore, a patient could meet criteria for disease flare and remain a PedACR responder at the same time.

For example, a subject who was a PedACR 90 responder could meet the criteria for flare (30 % worsening in 3 out of 6 criteria, minimum of 2 active joints, and improvement in no more than 1 JRA core criterion) and could still remain a Ped ACR 70, or Ped ACR 50, or Ped ACR 30 responder, depending on the degree and variables of worsening. In other words, at the time when subjects with JRA flares were withdrawn from the DB phase they could remain PedACR responders (although could lower to a less stringent response group) compared to their baseline prior to treatment with adalimumab in the OL-LI phase.

The aim of efficacy assessment in the OLE-BSA phase was to examine the continued benefit of treatment with adalimumab. Because the benefit of treatment had started in the OL-LI phase, the Sponsor elected to consider the observed PedACR responses at the end of the DB phase (compared to OL-LI baseline) as the baseline response rates for the beginning of the OLE-BSA

phase. Such approach, although it includes subjects who flared, captures the effect of adalimumab from the beginning of treatment without discounting the clinical benefit gained in the OL-LI phase. On the other hand, this approach also takes into consideration some loss of response that occurred in some patients during the DB phase.

There were no pre-specified conditions for analysis of the OLE-BSA phase hence no hypothesis testing was entertained in the analysis. The results of the OLE-BSA phase are all descriptive data showing the proportions of subjects with different degrees of PedACR response at different time points. When evaluating the results of the OLE-BSA phase it is important to understand that the duration of each subject's participation in this phase varied depending on the time when they entered the OLE-BSA phase and when they entered the OLE-FD phase. Thus, each subject could participate in the OLE-BSA phase for any duration up to 136 weeks. Four analyses with different methods of imputation were performed by both the Sponsor and the Agency to investigate the results of the OLE-BSA phase:

1) An analysis where the numerator reflected the number of PedACR responders and the denominator reflected the number of subjects who came for evaluation at a particular time point. This analysis was the original analysis submitted by the Sponsor and demonstrated high response rates approaching 100% among the PedACR 30 responders. Although informative, this analysis did not include all study participants at the time of evaluation which could lead to a potential bias of overestimate of the response rates since non-responders may be less likely to keep their clinic appointments.

The Division requested the Sponsor re-analyze their data to include all study participants in the analysis for each time point. Analyses #2 and #3 below were submitted by the Sponsor in response to this request.

2) An analysis where the numerator reflected the number of responders and the denominator reflected all subjects who were study participants for a particular visit, regardless of whether they kept their appointment or not. In this analysis, the missing values for subjects who missed their appointments during the time of their study participation were imputed in the numerator by LOCF. The graphic representations for this analysis are presented in the APPENDIX A.

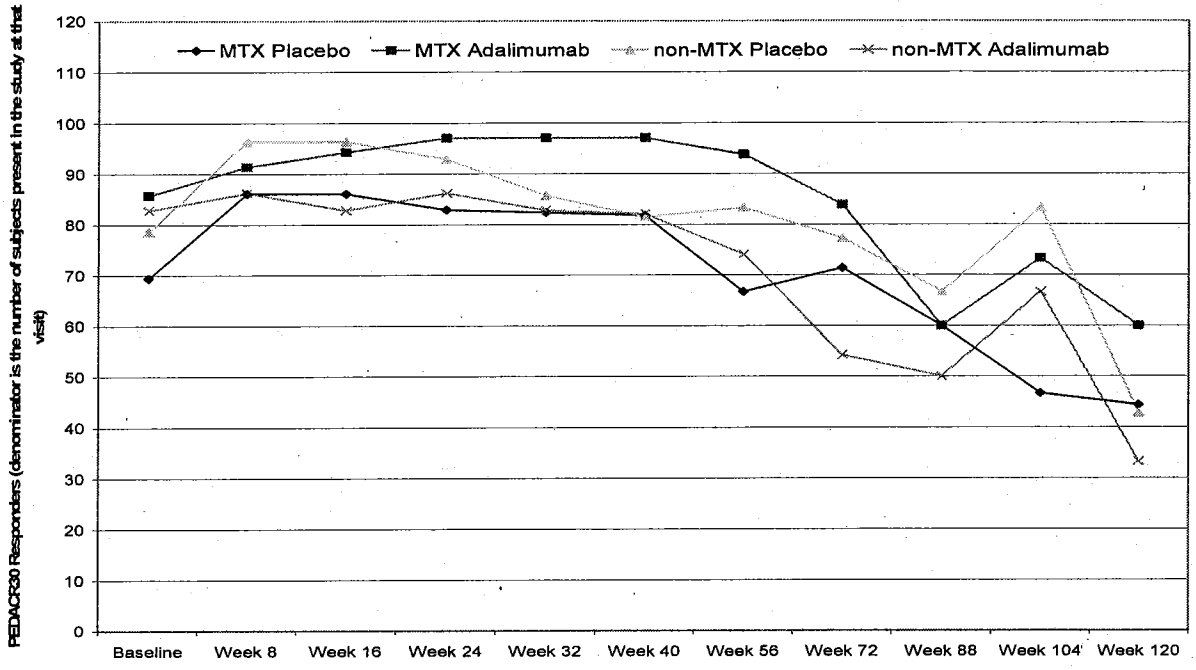
3) An analysis where the numerator reflected the number of responders (missing values imputed by LOCF) and the denominator reflected all subjects who received at least one dose of the study drug in the OLE-BSA (the denominator was kept constant and was based on the number of study participants enrolled in each group). In this analysis, the LOCF method was used to impute the data in the numerator not only for the missing visits for each individual during the time of his/her study participation but also for all visits up until the last observation at week 136 regardless of the actual time of study participation for each individual. This analysis was conducted and submitted by the Sponsor as an additional analysis in response to the Agency's request. This analysis resulted in a dense

imputation of data in the numerators and denominators throughout the study but more so toward the end of the OLE-BSA phase which made it difficult to interpret the results. For example, at week 120, the observed number of PedACR30 responders in the non-MTX stratum was 5 (Sponsor's Table 53, p. 288, CSR) and the number of responders with imputation was 51 (Sponsor's Table 7, response to IR from July 31, 2007).

4) An analysis where the numerator reflected the number of responders at each time point (study visit) without imputation for missing data and the denominator reflected the number of study participants at each time point regardless of their appearance for a particular clinic visit. This analysis was performed by the Agency to test the robustness of the observed efficacy results in the OLE-BSA phase. The results of the Analysis# 4 were similar to the results of the analysis #2 except the LOCF imputation method in the numerator (the number of responders) was not used in this analysis. The graphic representations for both #2 and #4 analyses are presented for comparison in the APPENDIX A.

Figure 5 shows PedACR 30 response maintenance in the OLE-BSA phase according to analysis #4. Refer to APPPENDIX A for graphic representations of PedACR 50, 70, and 90 responses. Although all subjects were treated with either adalimumab or the combination of adalimumab and MTX in the OLE-BSA phase, four treatment arms are graphed in Figure 5 to examine differences in response maintenance between the groups receiving continued adalimumab therapy (adalimumab groups) and the groups whose treatment with adalimumab was interrupted in the DB phase (placebo groups).

Figure 5. Maintenance of PedACR 30 responses in OLE-BSA phase.



Small number of subjects continued their study participation beyond week 88: n=15 in MTX group, n=15 in the combination of group, n=12 in the placebo group, and n=9 in the adalimumab monotherapy group; therefore, the responses beyond this point vary significantly since the percentage weight for each subject increased while decreasing the response rates at the time points toward the end of the OLE-BSA phase. Refer to APPENDIX A, Table A for proportions of PedACR responders in OLE-BSA according to analysis #4.

Several conclusions can be made from the analysis of maintenance of clinical benefit in the OLE-BSA phase:

1. At the baseline of the OLE-BSA phase the response rates were lower in the groups treated with placebo in the DB phase owing to treatment interruptions in those groups. The response rates were then regained by week 8 in all the groups and further maintained throughout weeks 56-72. The appropriately conservative analysis of the observed responders on the denominator of all study participants (#4) showed that the response rates remained substantial, demonstrating maintenance of clinical benefit from the treatment with adalimumab alone or in combination with MTX in the majority of patients.

2. A decline in response was observed in all groups after weeks 56-72, partially due to a possible escape from the therapeutic effect with time and partially due to the fact that fewer subjects participated in the study beyond week 72 and the percentage weight for

each subject increased while decreasing the response rates at the time points toward the end of the OLE-BSA phase.

3. Overall, the clinical benefit of adalimumab therapy was maintained after 13 months of treatment in the majority of patients who restarted their treatment in the OLE-BSA phase and after >2 years of treatment in the majority of patients who continued their treatment throughout OL-LI and DB phases. Patients withdrawn from the adalimumab monotherapy in the DB phase (placebo group) were able to regain PedACR responses similar to those observed in patients treated with monotherapy without interruption. The highest response rates were maintained among patients continuously treated with combination of MTX and adalimumab.

OLE-FD phase: The OLE-FD phase was added to evaluate the efficacy of adalimumab treatment when administered every other week as a fixed dose subcutaneous injection of 40 mg to children weighing ≥ 30kg and 20 mg to children weighing <30 kg. Because the same patients who participated in the OLE-BSA area were enrolled in the OLE-FD phase (Tables 3-5), the efficacy evaluation in the OLE-FD phase was done through analysis of maintenance of the existing response to adalimumab given at 24 mg/m^2 of body surface area in the previous phases of the study. The efficacy of the fixed dose regimen was evaluated during the first 16 weeks in the OLE-FD phase. Of the 106 subjects who entered the OLE-FD phase, 102 subjects completed 16 weeks of treatment. To estimate the continued benefit achieved and maintained by these patients throughout the OLE-BSA phase and into the OLE-FD phase, the PedACR response rates of those 106 patients were investigated (Table 21). The Sponsor conducted two other analyses: longitudinal comparison of response rates between the OLE-BSA phase and the OLE-FD phase and analysis of responses based on the amount of drug received (exposure) in the OLE-FD phase (data not shown). The results of the Sponsor's analyses appeared consistent with the analysis shown in Table 21 and further supported the evidence of response maintenance in the OLE-FD phase.

Table 21. Proportions of subjects with PedACR responses in the OLE-FD phase.

Time	MTX stratum		Non-MTX straum	
	Same/decreased N=28	Increased N=31	Same/decreased N=25	Increased N=22
Ped ACR 30				
Week 0	24(86%)	29 (94%)	24(96%)	20(91%)
Week 16	23(82%)	27 (87%)	23(92%)	18 (82%)
Ped ACR 50				
Week 0	23(82%)	27(87%)	23(92%)	20 (91%)
Week 16	23(82%)	27(87%)	23(92%)	18(82%)
Ped ACR 70				
Week 0	21(75%)	25(81%)	21(84%)	19(86%)
Week 16	21(75%)	25(81%)	21(84%)	18(82%)

Data obtained from Sponsor's Tables 57-59, CSR
PedACR responses calculated on the OL-LI baseline

Table 21 shows that the subjects who already benefited from adalimumab treatment and tolerated it well in the first three phases of the study were able to maintain their PedACR responses regardless of the dose change upon switch to the fixed dose regimen.

When the dose switch occurred, 53 subjects had their doses increased, 50 subjects had their doses left the same, and only three subjects had their dose decreased. Therefore, all patients with a few exceptions were receiving the same or higher doses of adalimumab. The pharmacokinetics (PK) studies (refer to Dr. Garnett's review) demonstrated similar exposure to drug in the OLE-FD phase and the OLE-BSA phases. Although the fixed doses were not administered to an adalimumab-naïve population, the results from the PK studies and the observed maintenance of clinical benefit in the OLE-FD phase suggest that the efficacy of adalimumab when administered in fixed doses is similar to that observed with administration of adalimumab doses calculated based on body surface area.

6.1.6 Efficacy Conclusions

Analysis of the primary and secondary endpoints provides statistically significant and consistent support for the efficacy of adalimumab in children with polyarticular JRA. Sensitivity and subgroup analyses further support the clinical benefits of adalimumab.

Study DE038 provides the principal evidence demonstrating the clinical efficacy of adalimumab in children with poly-articular JRA. The response to therapy in this study was measured by two composite scores (ACR pediatric response criteria and JRA flare) constructed on the same JRA core set criteria reflecting signs and symptoms of poly-articular JRA. The following conclusions can be drawn from the results of this study:

1. In the OL-LI phase, the onset of clinical benefit of adalimumab treatment was observed as early as after 2-4 weeks of treatment and improvement in all parameters of the JRA core set criteria was observed. At week 16, PedACR 30 response reached 94% in subjects treated with the combination of MTX and adalimumab and 74% in subjects treated with adalimumab monotherapy.
2. The primary analysis of flare rates in the DB randomized withdrawal phase demonstrated statistically significant superiority of adalimumab monotherapy over placebo in maintenance of clinical benefit among the enriched population of PedACR 30 responders in children with poly-articular JRA (71% vs 43%). Similarly, subjects treated with the combination of MTX and adalimumab demonstrated statistically significantly fewer flares than the subjects treated with MTX alone (65% vs 37%). The longevity of response was statistically significantly superior in subjects treated with adalimumab monotherapy or the combination of adalimumab and MTX than in subjects treated with placebo or MTX alone.
3. In the OLE-BSA phase, the response to therapy was further regained and maintained in the majority of subjects treated with adalimumab. Some decline of the treatment response was observed over time, likely due to the combination of an escape from the therapeutic effect in some subjects and the decreasing number of subjects whose study participation extended beyond week 72 in the OLE-BSA phase.
4. The response rates were further maintained after switch to the fixed dose regimen in the OLE-FD phase among subjects who previously benefited from adalimumab treatment.

Overall, the data presented in the Sponsor's submission support the proposed claim that treatment with adalimumab alone or in combination with MTX reduces signs and symptoms of JRA in patients aged 4-17 years with moderately to severely active poly-articular JRA [redacted] The efficacy of adalimumab treatment in children who failed previous biologic treatment(s) was not studied in study DE038.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety assessment of adalimumab was based on the dataset that included all subjects who received at least one dose of study drug in any of the four phases of the study. Safety data from the original submission were supplemented by 120-day safety update received on Aug 20, 2007 (four months into review cycle). The cut off date for the reported safety data for the original submission was Aug 1, 2006 and included 16 weeks of safety data from the OLE-FD phase. The cut off date for the reported safety for the 120-day update was March 15, 2007 and provided data up to at least week 48 of the OLE-FD phase.

As outlined above, study DE038 was a multi-center study stratified by MTX treatment, in subjects with JRA whose baseline demographic characteristics and disease activity were

representative of the patients with poly-articular subtype JRA seen in clinical practice. Although this study overall provided a reasonable safety assessment of adadlimumab as it is likely to be used in clinical practice, there was one limitation to the interpretation of the safety data. All subjects were exposed to the study treatment for the first 16 weeks of the OL-LI phase and some of the subsequent adverse events that occurred in the beginning of or during the DB phase in the placebo-treated subjects could, in fact, be delayed AEs related to the previous adalimumab exposure. Additionally, the DB phase time was shortened (<32 weeks) for those who were treated with placebo and flared. Thus, in this review, the comparison between the study drug and placebo was carried out with the understanding that the direct placebo comparison was limited owing to the design of the study.

7.1.1 Deaths

No deaths occurred in the study throughout the duration of OL-LI phase, DB phase, OLE-BSA phase, and the 48 weeks of the OLE-FD phase.

7.1.2 Other Serious Adverse Events

Serious AEs (SAE) were reported to the Sponsor by telephone within 24 hours of occurrence or notification of the site. An SAE was defined as any event that met any of the following criteria:

- death
- life-threatening
- hospitalization
- prolongation of hospitalization
- congenital anomaly
- persistent or significant disability/incapacity
- important medical event requiring medical or surgical intervention to prevent serious outcome
- spontaneous abortion
- elective abortion.

A total of 34/171 subjects developed 54 SAEs (excluding one subject who fell and had a possible concussion prior to receiving the study treatment) during the observation period up to week 16 of the OLE-FD phase.

Of the 52 events associated with treatment with adalimumab with or without MTX (Tables 22-23), 8/52 (15%) events comprised serious infections (2- H. Zoster, 1-H. Simplex, 1-pharyngitis, 1-urinary tract infection, 1-pneumonia, 1-bronchopneumonia, 1 viral infection) and 3 (6%) were events of appendicitis. Other SAEs occurring while on adalimumab treatment included 5 gastrointestinal events (in two subjects: #5205 and #5202), 1 fracture, 1 accidental injury, 1 worsening of previous hydrocephalus, 1 elective abortion, and 4 events of cytopenia (subject #1203). The rest of the events included 11 (21%) JRA flares requiring hospitalization, 13 (25%) events of planned in-patient treatments for complications of long-standing arthritis or co-morbid conditions, and 4 (8%) events of tonsil-and adenoidectomies.

There were no SAEs associated with treatment with placebo alone. Two events (gastroduodenitis and retinal detachment) were associated with treatment with MTX alone; the case coded as retinal detachment was, in fact, a planned ophthalmologic procedure performed for treatment of a previous retinal detachment occurred prior to study participation.

Overall, there were 8 serious infections in the study. See further discussion on serious infections including Herpes viruses' infections in Section 7.1.3 below. Notably, 46% of SAEs were either acute or chronic complications of the underlying arthritis. None of the observed SAEs were unexpected; occurrence of all kinds of infections and serious blood dyscrasias are known adverse events associated with adalimumab and are included in the current label for adalimumab. Occurrence of flares of underlying disease, surgical procedures for complications of JRA or complications and interventions for other comorbid conditions are to be expected in this patient population.

As submitted in the 120-day safety update, three additional SAEs (JRA flare, diabetic ketoacidosis, and planned intervention for breast reduction) occurred during the period from Week 16 to Week 48 of the OLE-FD phase.

Table 22. Proportion of subjects developing serious adverse events in study DE038.

	MTX		Non-MTX	
	Adalimumab		Adalimumab	
OL-LI	3/85 (3.5%)		5/86 (6%)	
	Placebo	Adalimumab	Placebo	Adalimumab
DB	2/37 (5%)	3/38 (8%)	0/28	1/30 (3%)
	Adalimumab		Adalimumab	
OLE-BSA	13/71 (18%)		8/57(14%)	
OLE-FD	1/59 (2%)		4/47(8%)	

4 subjects developed more than 1 SAEs during two phases of the study.

Table 23. Listings of serious adverse events in study DE038.

Subject #	Gender/ age	Onset day	Resolution day	Event[1]	Intervention	Outcome/ study drop out
OL LI						
MTX + Adalimumab						
1203	F/9	-1 17	4 31-40	**Leuko-, neutropenia.** **Leuko-, neutropenia.**	Adalimumab discontinued	Patient with h/o recurrent leucopenia prior to study enrollment. Withdrawn from the study
5302	F/7	57	107	Elevated Liver Enzymes, **JRA flare**	Adalimumab discontinued. Hospitalization for JRA flare	Withdrawn from study for elevated LFTs, flared with JRA 1 mo later
7102*	F/17	82	91	**Femur fracture**	Hospitalization	Patient with h/o osteopoprosis. Missed visits at weeks 12 and 14, randomized to DB at week 16
Non-MTX + Adalimumab						
5402	M/12	63/93/105	81/96/108	**JRA flare X 3**	Hospitalization	Withdrawn from the study
5301	F/10	112	122	**JRA flare**	Hospitalization	Withdrawn from the study/not randomized into DB phase at week 16
5501	F/8	107	107	**JRA flare**	Hospitalization	Withdrawn from the study
5104	F/15	62 post OL-LI	76	JRA flare, **Herpes simplex, genital**	Subject discontinued from the study for JRA flare. Hospitalization for H. simplex	Subject treated with corticosteroids for JRA flare, developed H. simplex 21 days after discontinuation of the study drug; therefore was withdrawn from the study
9202	F/16	56	147	**Pneumonia**	Hospitalization	Treated with IV antibiotics, withdrawn from the study
DB						
MTX+ placebo						
4104	F/7	117	121	**Gastroduodenitis**	Hospitalization	Continued in the study
7108	F/11	175	175	**Retinal detachment** in patient with chronic uveitis	Hospitalization	Planned intervention for the eye condition, continued in the study
MTX + adalimumab						
5203**	M/10	348	359	**Appendicitis**	Hospitalization	Appendectomy, continued in the study
5205**	F/16	253	309	**Abdominal pain, vomiting**	Hospitalization	Resolved, continued in the study
7102*	F/17	168 post OL-LI	176	**Injury** to the previously fractured leg	Hospitalization	Discontinued from the study (sponsor coded the reason as "other")
Non-MTX +adalimumab						
3105**	F/17	169	225	**UTI**	Hospitalization	Treated with a/b, continued in the study
OLE-BSA						
MTX + adalimumab						
5203**	M/10	625	952	**JRA flare**	Hospitalization	Treated with steroids, leflunomide; resolved
5205**	F/16	557	648	**Abdominal pain, hematochezia** (1 episode)	Clinical investigation did not reveal any cause	Resolved; concurrent medications included: rofecoxib, MTX, prednisone, ethinylestradiol, levonorgestrel
3103	F/4	500	541	**Adenoidal and tonsillar**	Hospitalization	Tonsillectomy and

				hypertrophy		adenoidectomy
3106	F/16	721/ 771	757/ 820	**JRA flare X 2**	Hospitalization	BL knee synovectomy
3104	F/12	703	717	**Pharyngitis**	Hospitalization	Treated with a/b, resolved
1703	F/8	522	526	**Appendicitis**	Hospitalization	Appendectomy
6102	M/7	428	430	**JRA flare**	Hospitalization	Multiple intra-articular injections
5506	F/10	526	533	**Herpes Zoster**	Hospitalization	Treated with Acyclovir, resolved
4101	M/13	387/ 401/ 456/ 765	390/ 404/ 460 768	**JRA** (JRA complications X 4)	Hospitalization	Right and left hand surgical reconstruction, one intervention for ulna nonunion, total of 4 planned surgical interventions
4107	F/13	800	837	**Osteoarthritis** (Planned treatment of hip OA)	Hospitalization	Total endoprosthesis of the hip joint
4102	F/14	450/ 778	456/ 781	**JRA** (JRA complications X 2)	Hospitalization	Planned surgical interventions for hand reconstruction
704	M/4	651	665	**JRA flare** with systemic signs and pericarditis	Hospitalization	Treated with steroids with resolution
1202	F/9	466	476	**Viral infection** complicated by worsening of **hydrocephalus** in a subject with chronic VP shunt for obstructive hydrocephalus	Hospitalization	Treatment with a/b, VP shunt revision for malfunction. Subject was withdrawn from the study
Non-MTX + adalimumab						
3105**	F/17	652	670	**Herpes Zoster**	Hospitalization treated with acyclovir.	Resolved; study drug temporarily discontinued, then restarted
5107	F/7	421	437	**JRA** (JRA complications)	Hospitalization	Serial casting, orthoses placement for treatment of chronic bilateral knee contractures
5202	F/14	523	647	**Malabsorption**	Hospitalization Low fructose diet	Resolved
6104	M/6	660	669	**Bronchopneumonia**	Hospitalization	IV a/b with complete resolution. Study drug temporarily dc-ed, then restarted
5403	F/14	220/ 454	289/ 609	**Speech disorder** **Joint dislocation**	Hospitalization	Inpatient intensive speech therapy in a patient with previous history of speech disorder Planned surgery for habitual patella dislocation
5504	F/8	797	837	**Joint contracture**	Hospitalization	Planned surgery for finger contracture
1304	M/11	712	713	**Adenoidal and tonsillar hypertrophy**	Hospitalization	Tonsillectomy and adenoidectomy
1102	F/17	457	475	**Elective abortion**	Elective abortion	Study drug was discontinued on Day 461
OLE-FD* **						
MTX + adalimumab						
3201	M/12	1015/ 1265	1071/ 1416	**JRA** (JRA complication) JRA (severe hip arthritis)	Hospitalization	Hospitalization for hip traction plus treatment with increasing dose of methylprednisolone Discontinued for the second SAE of recurrent hip arthritis
Non-MTX + adalimumab						
1306	F/7	873	875	**Appendicitis**	Hospitalization	Appendectomy

5105	F/10	950	968	**Knee deformity**	Hospitalization	Planned surgical treatment of bilateral genu valgus
1616	F/14	1031	1035	**Diabetic ketoacidosis** due to self-discontinuation of oral insulin	Hospitalization	Previous history of diabetes, appropriate treatment was given
1002	F/16	1218	1218	**Breast reduction**	Surgical procedure	Elective breast reduction, study drug temporarily discontinued, then restarted after surgery

Data sources: Table 89 from the Study report, p.381, narratives of SAEs from Section 14.3_3, Clinical research forms (CRFs) for subjects experiencing SAEs in the OL-LI and DB phases of the study.
[1] events meeting definition of SAE are identified in bold
* subject developed more than one SAEs during OL-LI and DB phases of the study (n=1)
** subject developed more than one SAEs during DB and OLE-BSA phases of the study (n=3)
***All subjects who developed SAE in the OLE-FD phase remained on the same dose except subject #1306 whose dose was increased by 10 mg.

Serious infectious adverse events (AEs).

There were 11 serious infectious AEs (Table 24) including 3 events of appendicitis that occurred in 10/171 (6%) subjects while on treatment with adalimumab with or without concomitant MTX. None of the subjects treated with placebo or MTX alone in the DB phase developed any serious infections. Excluding appendicitis, five serious infections occurred in 4 subjects in non-MTX stratum resulting in a 5% (4/86) incidence of infectious SAEs associated with adalimumab monotherapy, and 3 serious infections occurred in the MTX stratum resulting in a 4% (3/85) incidence of infectious SAEs associated with the combination of MTX and adalimumab.
None of the infectious SAEs were unexpected; no SAEs associated with opportunistic infections, including mycobacterial infections, occurred in the study. Refer to Section 7.1.3 for discussion of Herpes virus-related infections.

Table 24. Serious infectious adverse events in study DE038.

Subject #	Gender/age	Onset day	Resolution day	Event	Intervention	Outcome/ study drop out
OL LI						
Non-MTX + Adalimumab						
5104	F/15	62 post OL-LI	76	**Herpes simplex, genital**	Hospitalization for H. simplex	Subject treated with corticosteroids for JRA flare, developed H. simplex 21 days after discontinuation of the study drug; therefore, was withdrawn from the study
9202	F/16	56	147	**Pneumonia**	Hospitalization	Treated with IV antibiotics, withdrawn from the study
DB						
MTX + adalimumab						
5203	M/10	348	359	**Appendicitis**	Hospitalization	Appendectomy, continued in the study
Non-MTX +adalimumab						
3105	F/17	169	225	**UTI**	Hospitalization	Treated with a/b, continued in the study
OLE-BSA						
MTX + adalimumab						
3104	F/12	703	717	**Pharyngitis**	Hospitalization	Treated with a/b, resolved
1703	F/8	522	526	**Appendicitis**	Hospitalization	Appendectomy
5506	F/10	526	533	**Herpes Zoster**	Hospitalization	Treated with Acyclovir, resolved
1202	F/9	466	476	**Viral infection** complicated by **hydrocephalus** in a subject with chronic VP shunt for obstructive hydrocephalus	Hospitalization	Treatment with a/b, VP shunt revision for malfunction. Subject was withdrawn from the study
Non-MTX + adalimumab						
3105	F/17	652	670	**Herpes Zoster**	Hospitalization treated with acyclovir.	Resolved; study drug temporarily discontinued, then restarted
6104	M/6	660	669	**Bronchopneumonia**	Hospitalization	IV a/b with complete resolution. Study drug temporarily discontinued, then restarted
OLE-FD						
Non-MTX + adalimumab						
1306	F/7	873	875	**Appendicitis**	Hospitalization	Appendectomy

7.1.3 Dropouts and Other Significant Adverse Events

Study Dropouts:

According to the study protocol, subjects were to be withdrawn from the study if any of the following occurred:

- Clinically significant abnormal laboratory results as determined by the Sponsor.

- Clinically significant deterioration of the subject's medical status.
- The Investigator believed it was in the best interest of the subject.
- The parent or legal guardian requested withdrawal of the subject from the study.
- A selection criteria violation was noted after the subject started study drug.

Subjects who prematurely discontinued from the study and had received at least one dose of study drug were not replaced. The date of the last dose and reason for premature discontinuation was recorded on the appropriate CRF. All subjects were examined one month after their last injection of study drug.

7.1.3.1 Overall profile of dropouts

The total number of dropouts for all four phases of study DE038 is shown in Table 25. Refer to Section 7.1.3.2 for discussion of study dropouts for adverse events.

Twelve subjects discontinued prematurely from the OL-LI phase; these subjects were primarily from the non-MTX stratum (9 vs 3). Of the 9 subjects from the non-MTX stratum, six subjects discontinued for lack of efficacy.

Twenty six subjects completed the OL-LI phase but did not enroll in the DB phase. From the non-MTX stratum three subjects developed JIA flares towards the end of OL-LI phase and four other subjects discontinued from the study for the lack of efficacy. Protocol deviations necessitating withdrawal from the study occurred in one patient in non-MTX stratum (fewer than required number of swollen joints at screening) and in one patient from the MTX stratum (noncompliance with study visits and medications). Fifteen subjects whose reason for discontinuation was coded as "other" (9 in the non-MTX and 6 in the MTX strata) were not randomized in the DB phase primarily for not meeting PedACR 30 criterion and lack of efficacy. Two subjects from non-MTX stratum withdrew consent for non-compliance and lack of efficacy respectively.

In the DB phase, one subject from the non-MTX stratum was discontinued from the study because their dose was not timely increased to correspond with subject's growth. From the MTX stratum, three subjects discontinued for the reasons coded as "other": two subjects were withdrawn due to protocol violations of inadequate joint assessment and randomization by error and one subject with previous history of dwarfism and osteoporosis developed a serious AE of femoral fracture and missed her appointments at weeks 12 and 14 in the OL-LI phase, was randomized into DB at week 16 but then had an accidental traumatic injury (Sponsor's response from October 31, 2007) during the DB phase; therefore, was discontinued from the study by Sponsor's request. One subject withdrew consent at week 40 without further explanation.

Twenty two subjects did not complete the OLE-BSA phase. Three subjects treated with MTX and adalimumab (formerly treated with placebo in MTX stratum) and one subject treated with adalimumab alone (formerly treated with placebo in non-MTX stratum) discontinued due to lack of efficacy. Of the 9 subjects who withdrew consent, two went into remission and discontinued

the study drug (one was treated with adalimumab alone and another was receiving combination of the adalimumab and MTX); 3 subjects discontinued for fear of risks associated with the study medication, 2 provided no explanations and 2 other subjects discontinued for the reasons unrelated to the study protocol. Of the 6 subjects whose reasons for discontinuation were coded as "other", 5 patients had to be withdrawn from the study because they were not willing to participate in the fixed dose phase (protocol condition) and one subject discontinued because they went into remission. The protocol violation necessitating withdrawal from the study was pregnancy in a 17 y/o study participant from the non-MTX stratum (also refer to Section 7.1.3.2).

Of the 106 subjects entering the fixed dose phase of the study, 10 subjects discontinued the study prematurely by week 48. From the non-MTX stratum, two subjects were lost to follow up and one subject was discontinued for non-compliance to protocol and unsatisfactory drug response. One subject withdrew consent; 3 subjects whose discontinuations were coded as "other" discontinued their study participation for administrative reasons.

Table 25. Patients who prematurely discontinued their participation from study DE038 (study dropouts).

OL LI phase (16 weeks)	All patients	Non-MTX		MTX	
All randomized patients, n(%)	171	86		85	
Dropouts before week 16, n(%)	12 (7%)	9 (10%)		2(2%)	
Adverse event, n(%)*	4 (2%)	2 (2%)		2 (2%)	
Lack of efficacy, n(%)	6 (3.5%)	6 (7%)		0	
Withdrawal of consent, n(%)	1 (<1%)	0		1(1%)	
Lost to follow up, n (%)	1(<1%)	1(1%)		0	
Patients who did not enroll into DB phase, primary reason for not enrolling	26 (15%)	19 (22%)		7(8%)	
Adverse event, n	3	3		0	
Lack of efficacy, n	4	4		0	
Other, n	15	9		6	
Protocol violation, n	2	1		1	
Withdrew consent, n	2	2		0	
DB phase (32 weeks)	All patients	Non-MTX		MTX	
		Adalimumab	Placebo	Adalimumab	Placebo
All randomized patients, n(%)	133	30	28	38	37
Dropouts before week 48, n(%)	5(4%)	1(3%)	0	3(8%)	1
Other, n(%)	3(2%)	0	0	3(8%)	0
Withdrawal of consent, n(%)	1(<1%)	0	0	0	1(3%)
Protocol violation, n(%)	1(<1%)	1(3%)	0	0	0
OLE-BSA (up to 136 weeks)	All patients	Non-MTX		MTX	
		Adalimumab*	Placebo*	Adalimumab*	Placebo*
All enrolled patients	128	29	28	35	36
Dropouts prior to the beginning of OLE-FD phase, n (%)	22(17%)	5(17%)	5(18%)	4(11%)	8(23%)
Adverse event, n (%)	2	0	1	0	1
Lack of efficacy, n (%)	4	0	1	0	3
Withdrawal of consent, n (%)	9	4	2	1	2
Other, n (%)	6	0	1	2	3
Protocol violation, n(%)	1	1	0	0	0
OLE-FD (16 weeks)	All patients	Adalimumab		MTX plus adalimumab	
		Increased dose	Same or Decreased dose		Increased dose
All enrolled patients, n(%)	106	22	25	106	22
Dropouts before week 48, n(%)	10(9%)	5(23%)	2(8%)	10(9%)	5(23%)
Adverse event, n	3	0	1	3	0
Other, n	3	2	1	3	2
Lost to follow up, n	2	2	0	2	2
Withdrew consent, n	1	0	0	1	0
Protocol violation, n	1	1	0	1	1

7.1.3.2 Adverse events associated with dropouts

Of the adverse events leading to premature discontinuation of study participation associated with the effects of adalimumab, leucopenia and neutropenia and LFT elevations occurred with combination of MTX and adalimumab and are known to be associated with both of these drugs. Menorrhagia was of moderate severity and prompted discontinuation of adalimumab in a 17 y/o female patient, subsequent development of pneumonia precluded restart of adalimumab treatment in the same patient. Both increased risk for infections and menstrual disorder are currently indicated in the product label. Creatine phosphokinase (CPK) elevations have been previously observed with TNF-inhibitors but were somewhat unexpected in this study. A detailed exploration of changes in CPK is further described in Section 7.1.3. No dropouts for AEs were observed in the DB phase.

Overall, the early dropouts due to adverse events observed in the OL-LI phase of the study reflected already known effects of adalimumab treatment. The adverse events observed in the extension phases primarily included flares of the underlying disease which is not unexpected in the given patient population.

Table 26. Subjects who prematurely discontinued their study participation due to adverse events.

Subject #	Gender/ age	Onset day	Duration, days	Reason for drop out	Outcome after discontinuation of the study treatment
OL-LI					
MTX + adalimumab					
1203	F/9	17 17	15 24	Leukopenia Neutropenia	resolved
5302*	F/7	57	50 29	ALT increased AST increased	resolved
Non-MTX + adalimumab					
9202	F/17	16 56	43 92	Menorrhagia (Pneumonia)	resolved
1618	F/11	68	Sporadic	Dizziness CPK elevation	resolved
Two subjects treated with adalimumab in the non-MTX stratum developed JRA flares requiring hospitalization and were later discontinued from the study					
5104	F/15	40	>73	JRA flare	Treated with steroids for JRA flare. H. simplex genital occurred ~ 1 mo after discontinuation of the study treatment, resolved with antiviral treatment
5402	M/13	63	19	JRA flare	Required hospitalization and treatment with standard of care
Completed OL-LI, did not enroll in the DB phase					
Non-MTX + adalimumab					
1701	F/17	96	34	Daily headaches, JRA flare	Required standard of care treatment
5501	F/8	107	>1	JRA flare	Required hospitalization and standard of care treatment Patient was also noticed to have CPK elevation while on treatment
5301	F/10	112	>11	JRA flare	Required hospitalization and standard of care treatment
OLE-BSA					
Non-MTX +adalimumab					
7107	F/9	467	>72	JRA flare	Required standard of care treatment
MTX + adalimumab					
1202	F/9	466	11	Viral infection complicated by VP shunt malfunction	Required hospitalization and VP shunt revision. Viral infection resolved with IV fluids
OLE-FD					
Non-MTX + adalimumab					
5107	F/7	1051	unknown	JRA flare	Required treatment for the flare
MTX+adalimumab					
704	M/4	1166	>79	JRA flare	Required standard of care treatment
3201	M/12	1265	unknown	Recurrent hip arthritis due to JRA	Required hospitalization

Data from Table 90, p. 386 of CSR and 120-day safety update.

7.1.3.3 Other significant adverse events.

Infections

Since all patients were exposed to adalimumab in the OL-LI phase and since overall in the study the duration of adalimumab exposure was longer than the duration of placebo exposure, the comparison between drug and placebo is limited owing to the study design (Section 7.1).

It is well known that the TNF blockers are associated with immunosuppression related their mechanism of action, therefore, infectious complications are characteristic for this class of biologic agents. The most common infections occurring in 2 or more study subjects are shown in the Tables 27-28.

Overall, the most common infections were upper respiratory infections and viral infections occurring in up to 20% of children with adalimumab monotherapy, followed by gastrointestinal infections and infestations. Infections of other systems such as otitis media, urinary tract infections, integumental (skin and nails) infections of fungal and bacterial origins were observed as well.

The four treatment arms in the DB phase allow a comparison of infectious AE incidences in subjects treated with placebo, MTX alone, adalimumab alone, and combination of MTX and adalimumab. The incidence of any infectious AEs was lowest in the placebo group from the non-MTX stratum (39%) and highest in the subjects treated with adalimumab alone (63%). Subjects treated with combination of adalimumab and MTX had infectious AE rate comparable with that of adalimumab alone, but slightly lower numerically (58%).

Of the infections of the lower respiratory tract, the two cases of pneumonia and two cases of bronchitis were observed in subjects treated with adalimumab alone, whereas one case of tracheobronchitis was observed in subjects treated with the combination of MTX and adalimumab in the OL-LI phase (data not shown, obtained from Sponsor's Table 14.3_1.3.1.1).

Notably, H. simplex occurred in ~4 % of subjects receiving adalimumab regardless of MTX treatment in the OL-LI phase. In the DB phase, two events of Herpes infections were reported among the subjects treated with adalimumab alone (one coded as Herpes simplex in Table 27, another coded as Herpes virus infection- data not shown, Sponsor's source Table 14.3_1.3.1.2); one case of H. Simplex occurred among subjects treated with combination of adalimumab and MTX, and two cases of H. Simplex were reported among subjects treated with MTX alone. These data compare with no subjects presenting with herpetic infections among those treated with placebo (Table 27).

Five subjects treated with adalimumab alone in the OL-LI phase developed streptococcal infections (3 cases of streptococcal pharyngitis, 1 beta-hemolytic streptococcal infection, 1 pyoderma streptococcal); one case of streptococcal pharyngitis was reported among subjects treated with combination of MTX and adalimumab. Three additional cases of streptococcal pharyngitis occurred in the DB phase of the study.

The few cases of influenza appeared to be equally distributed among the different treatment regimens; cases on treatment did not exceed cases on placebo (data not shown, Sponsor's source Table 14.3_1.3.1.2).

Table 27. Infectious adverse events occurring in 2 or more subjects in OL-LI, DB, OLE-BSA phases of study DE038.

Adverse events by preferred term	OL-LI		DB				OLE-BSA	
	MTX+ ada^ N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N=57
Proportion of subjects with one or more events, n (%)	37(44)	39(45)	19 (51)	22(58)	11(39)	19(63)	56 (79)	41(72)
Upper respiratory tract infection	6 (7)*	9* (10)	4 (11)	5 (13)	5 (18)	6 (20)	20 (28)	19(33)
Viral infection	6 (7)	7 (8)	2 (5)	6 (16)	3 (11)	6 (20)	14(20)	10(18)
Nasopharyngitis	6 (7)	2 (2)	4 (11)	5 (13)	3 (11)	0	9 (13)	4(7)
Pharyngitis	3 (4)	3 (4)	2 (5)	1 (3)	1 (4)	0	10(14)	4(7)
Pharyngitis streptococcal	1 (1)	3 (4)	1 (3)	0	1 (4)	1 (3)	3(4)	6(10)
Herpes Simplex	3 (4)	3(4)	2 (5)	1 (3)	0	1 (3)	2(3)	2(4)
Impetigo	0	2 (2)	0	2 (5)	0	1 (3)	2(3)	5(9)
Rhinitis	3(4)	2(2)	0	3(8)	0	2(7)	4(6)	2(4)
Sinusitis	5(6)	1(1)	0	2(5)	1(4)	0	7(10)	7(12)
Otitis media/ ear infection	1(1)	2(2)	1(3) 0	1(3) 1(3)	0 1(4)	0 1(3)	2(3) 4(6)	5(9) 0
Acute tonsillitis	2(2)	0	2(5)	1(3)	0	0	4(6)	0
Paronychia	0	2(2)	0	1(3)	0	2(7)	3(4)	1(<2)
Gastroenteritis	3(4)	4(5)	1(3)	0	0	0	2(3)	2(4)
Gastroenteritis viral	0	2(2)	1(3)	0	1(4)	0	1(1)	2(4)
Pneumonia	0	2(2)	NR	NR	NR	NR	0	2(4)
Bronchitis	0	1(1)	1(3)**	1(3)**	0	1(3)**	4 (6)	1(<2)
UTI	1(1)	0	0	1(3)	1(4)	1(3)	5(7)	4(7)

* combines referred terms "Upper respiratory infection" and "viral upper respiratory infection"
** combines preferred terms " bronchitis", "bronchitis viral", "bronchitis acute"
^ ada- adalimumab
Data obtained from DE038 Section 14.3, Table 14.3__1.3.6.1, Table 14.3_1.4.1 Table 93, page 393 of the study report.
Additional events occurring in 2 subjects include: dental caries (OL-LI); eye infection, influenza. Tinea pedis, folliculitis, infectious mononucleosis, Herpes Zoster, varicella (OLE-BSA).
NR- not reported

In the OLE-BSA phase, subjects were treated with either adalimumab alone or the combination of MTX and adalimumab. Analysis of AEs in this phase allows examining adverse events associated with chronic use of adalimumab. Overall, the rate of AEs was 79% in those treated with the combination and 72% in subjects treated with adalimumab alone. Upper respiratory tract infections and viral infections continued to be the most common AEs observed (nasopharyngitis as the leading reported category). The majority of the commonly occurring infections (Table 27), occurred at higher rate with the combination treatment. Notably, several infectious complications

happened to occur in association with adalimumab monotherapy, sometimes in rates exceeding those seen with the combination therapy, those included: streptococcal pharyngitis, otitis media, impetigo, and pneumonia.

To further examine any changes in rate of infectious AEs that may have occurred with increase in adalimumab dose when the dosing regimen was switched from BSA to a FD regimen by weight, AE rates were examined in **the OLE-FD phase** from the perspective of dose change (Table 28).

Table 28. Infectious AEs occurring in 2 or more subjects in OLE-FD phase.

	MTX		non-MTX		Overall	
	Same/ Decreased	Increased	Same/ Decreased	Increased	Same/ Decreased	Increased
	N = 28	N = 31	N = 25	N = 22	N = 53	N = 53
Proportion of subjects with any infectious AE, n (%)	14(50)	17(55)	11(44)	10(46)	25(47)	27(51)
AEs by preferred term						
Acute tonsillitis	0	2(6)	0	0	0	2(4)
Gastroenteritis viral	3(11)	0	0	0	3(6)	0
Herpes Simplex	1(4)	2(6)	0	0	1(2)	2(4)
Nasopharyngitis	1(4)	2(6)	1(4)	0	2(4)	2(4)
Pharyngitis	2 (7)	1 (3)	0	0	2 (4)	1 (2)
Rhinitis	1 (4)	1(3)	1(4)	2(9)	2(4)	3(6)
Sinusitis	1(4)	3(10)	1(4)	0	2(4)	3(6)
Upper respiratory tract infection	3 (11)	1(3)	4 (16)	3 (14)	7(13)	4(8)
Ear infection	1(4)	3 (10)	1 (4)	0	2 (4)	3 (6)
Viral infection	2(7)	1 (3)	2 (8)	5 (23)	4(8)	6 (11)
Viral upper respiratory tract infection	0	2(6)	0	1(4)	0	3(6)

Data obtained from Table 14.3__1.4.2.1.
Table 94, page 395, CSR (original submission)
Table 2.4_1.3.1 (120-day safety update)

Slightly higher rates of viral infections and viral URIs were observed in those whose dose of adalimumab was increased in the OLE-FD phase, although there were too few cases in each group to draw definitive conclusions. Also refer to Section 8.1 for discussion of dose change regimen.

Refer to APPENDIX B for listings of single infectious AEs in study DE038.

Conclusions on infectious complications:

Overall, the most common infectious AEs occurring with adalimumab treatment with or without MTX were those associated with the upper respiratory tract, primarily viral. Serious infections of

the lower respiratory tract (pneumonia, bronchopneumonia, bronchitis) were not as frequent, but were observed mainly with treatment with adalimumab monotherapy. Infections of the GI tract, ear, and urinary tract were primarily mild and moderate and required standard treatment or were self-limited. Of note, infections of skin, mucous membranes, and nails including both bacterial and fungal infections, were observed in association with adalimumab treatment; concomitant treatment with MTX did not seem to increase the rate of integumental infections.

Infections with Herpes Simplex and Herpes Zoster were observed in association with adalimumab treatment in every phase of the study. In the DB phase, four adverse events of herpetic infections were reported in subjects treated with adalimumab (three with adalimumab alone and one with the combination of adalimumab and MTX) compared with no such events among subjects treated with placebo. Thus, Herpes virus infections are associated with adalimumab treatment. This observation was also reported in the adult studies with adalimumab as well as in adult and pediatric studies with other TNF-blockers such as etanercept and infliximab.

Streptococcal pharyngitis was also observed among subjects treated with adalimumab. More cases of streptococcal pharyngitis were observed with long term treatment in the OLE-BSA phase (3/71- 4% treated with the combination of adalimumab and MTX vs 6/57 - 10% treated with adalimumab alone). Taken together with the higher rate of skin impetigo (DB in OLE-BSA phases) and occurrence of streptococcal pyoderma (OL-LI phase) it appears that the decreased immune defenses toward streptococcal infections may represent one other aspect of safety profile of adalimumab treatment in JRA population.

Injection site reactions

Owing to the subcutaneous route of administration, injection site complications occurred frequently with adalimumab treatment. The proportion of subjects with any injection site event was over 40% in the OL-LI phase, remained 37% in the DB phase and gradually decreased in the extension phases of the study (Table 29). The most frequently reported were reaction (14-16%), pain, burning and irritation at the injection site. The observed rate in study DE038 was higher than the injection site reactions rate seen in adults treated with adalimumab (8% for injection site reactions, 12% for injection site pain; Source: Humira® label). Overall, this rate of injection site reactions was comparable with the rate observed in clinical studies in children treated with another biological product etanercept (39% rate as indicated Dr. Rider's review of safety of etanercept in JRA).

Table 29. Injection site reactions occurring with adalimumab treatment in children with JRA in study DE038.

	OL-LI		DB				OLE-BSA		OLE-FD	
	MTX+ ada N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N=57	MTX + ada N=59	Ada N=47
Proportion of subjects with one or more events, n (%)	35(41)	37(43)	9(24)	14(37)	4(14)	11(37)	20(28)	18(32)	10 (10)	
Injection site reactions by preferred term, n (%)										
Reaction	15(18)	12(14)	1(3)	7(18)	1(4)	3(10)	8(11)	9(16)	1(2)*	1(2)*
Pain	13(15)	19(22)	6 (16)	7(18)	3(10)	5(17)	10(14)	6(10)	1+1*(3)	1(2)*
Burning	8 (9)	9(10)	2(5)	1(3)	0	4(13)	Not reported		Not reported	
Irritation	Not reported		Not reported				5(7)	5(9)	2(3)(6)**	2(4)(9)**
Discomfort	1(1)	0	Not reported				Not reported		Not reported	
Erythema	3(4)	2(2)	1(3)	2(5)	0	1(3)	Not reported		Not reported	
Hemorrhage	0	2(2)	0	1(3)	0	0	Not reported		Not reported	
Hypersensititvity	Not reported		1(3)	0	0	0	Not reported		Not reported	
Pruritis	1(1)	2(2)	0	1(3)	0	1(3)	Not reported		Not reported	
Rash	1(1)	0	Not reported				Not reported		Not reported	
Stinging	2(2)	0	Not reported				Not reported		Not reported	
Swelling	1(1)	0	Not reported				1(1)	0	1	0
Discoloration									1	0

Source for patient proportions (table 14.3_1.2.1.1, Tables 68-71 from the Study report, Source Tables 14.3_1.3.1.1-2, 14.3_1.4.1., and 14.3_1.4.2.1.
*occurred with increase in adalimumab dose
** occurred with increase in adalimumab dose in 6% and 9% subjects among those treated with increased dose of adalimumab in two strata (n=31 for MTX stratum and n=22 for non-MTX stratum)

Allergic hypersensitivity reactions

Several allergic hypersensitivity reactions occurred in children treated with adalimumab (Table 30). None of the allergic reactions were severe or serious. Overall, the 5-7% rate of non-serious allergic reactions in children treated with adalimumab was higher than that reported in adults (1%). The allergic reactions were primarily localized skin reactions at the administration site; a few cases of recurrent erythema appeared to occur in subjects who also developed anti-adalimumab antibodies.

Table 30. Allergic hypersensitivity reactions occurring with adalimumab treatment in children with JRA in study DE038.

	OL-LI		DB				OLE-BSA		OLE-FD	
	MTX+ ada N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N=57	MTX + ada N=59	Ada N=47
Proportion of subjects with one or more events, n (%)	7(8)	5(6)	0	2(5)	0	3(10)	4(6)	3(5)	0	2(4)
Allergic and hypersensitivity reactions by preferred term, n (%)										
Drug hypersensitivity	0	1(1)	Not reported							
Seasonal allergy	1(1)	1(1)	0	0	0	1(3)	2(3)	1(2)	Not reported	
Hypersensititvity	6(7)	4(5)	0	2(5)	0	2(7)	2(3)	2(3)	1(<2)	2(4)(9)*

Source for patient proportions: Tables 14.3_1.3.1.1-2, 14.3_1.4.1., and 14.3_1.4.2.1.
*occurred with increase in adalimumab dose (4% if calculated among all subjects in the group, 9% if calculated only among those whose dose was increased)

Skin disorders:

No serious or severe skin disorders occurred in the study. A few cases of dermatitis and urticaria resolved; there was one non-severe and non-serious case of bullous dermatitis. Notably, in the OLE-FD phase there were two cases of granuloma annulare. Cases of granuloma annulare have been reported in association with anti-TNF therapies, including adalimumab therapy in adults[3]. Occurrence of granuloma annulare is not currently reported in the adalimumab label. It is recommended to describe the occurrence of such event in the product label to inform treating clinicians of this potential uncommon event associated with adalimumab therapy.

Table 31. Skin disorders occurring with adalimumab treatment in children with JRA in study DE038.

	OL-LI		DB				OLE-BSA		OLE-FD	
	MTX+ ada N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N=57	MTX + ada N=59	Ada N=47
Skin and subcutaneous tissue disorders by preferred term, n (%)										
Dermatitis	0	2(2)	1(3)	1(3)	0	0	5(7)	0	1(2)*	0
Dermatitis allergic	3	0	Not reported				Not reported		0	1*
Dermatitis atopic	0	1	Not reported				Not reported		Not reported	
Dermatitis bullous	1	0	Not reported				Not reported		Not reported	
Dermatitis contact	1	0	0	0	0	1	Not reported		1*	1+1*
Erythema	0	3	1	0	2	0	1	0	Not reported	
Rash	5	5	1	1	0	2	5	4	2	1+1*
Rash papular	1	2	0	0	1	1	1	0	0	1
Urticaria	0	1	Not reported				1	1	1*	0
Granuloma annulare	Not reported		Not reported				Not reported		1	1*

*dose of adalimumab was increased
Source data: Tables 14.3_1.3.1.1-2, 14.3_1.4.1., and 14.3_1.4.2.1 from the original submission and Table 2.4_1.3.1 from the safety update

No malignancies occurred during the observation period of study DE038 as reported by the Sponsor up to week 48 of OLE-FD phase of the study.

Severe adverse events:

Table 32 shows the occurrence of severe AEs in study DE038. The vast majority of these severe adverse events were not unexpected and are indicated in the current adalimumab label; for example, severe bacterial and viral infections and severe injection site reactions. Some others are known complications of the underlying JRA or comorbid conditions. A case of severe myositis is described in more detail below. Also refer to Section 7.1.7 for a description of LFTs elevations.

Table 32. Severe AEs in study DE038.

	OL-LI		DB				OLE-BSA		OLE-FD	
	MTX+ ada N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N=57	MTX + ada N=59	Ada N=47
Neutropenia	1	1								
Pharyngitis		1								
Pneumonia		1								
Streptococcal pharyngitis		1								
JRA		1					2	1		1+1*
Injection site pain	1						1			
Femur fracture	1									
Increased AST	1								1*	
Increased ALT	1						1		1*	
Neck pain	1									
Appendicitis				1			1			1*
Injury				1						
Pain						1				1
Bronchopneumonia								1		
Herpes zoster							1			
Rheumatoid arthritis							1	1	2	
Myositis							1			
Osteoarthritis							1			
Metrorrhagia									1	
Breast enlargement										1
Viral infection										1*
Sinus infection									1*	

Data source: Tables 14.3_1.3.3.1; 14.3_1.3.3.2.1-2; 14.3_1.7.1; 14.3_1.7.2.1; Table 12 from 120-day safety update
* adalimumab dose was increased

Other medically significant events:

Several medically significant events were reported in the study. The Agency requested the Sponsor explain the circumstances and previous history under which the events occurred. A summary of the events and the respective explanations is presented below.

1) Epilepsy. A 7 y/o female child experienced several sporadic episodes of epilepsy (at least 3) during the OLE-BSA phase of the study. The patient had no previous history of seizure disorder and no other alternative explanations to the onset of seizure episodes were found. The subject was subsequently treated with Depakine.
2) Syncope. There were 5 cases coded as "syncope" during the study. None of the events were associated with loss of consciousness, each event appeared more as an episode dizziness or lightheadedness lasted one to a few minutes. One case was

associated with the first time injection administration in a subject in the OL-LI phase; four other cases occurred in the OLE-BSA phase and were associated with injection administration, stress and lack of breakfast, dizziness, and previous history of syncope. No apparent relation to adalimumab moiety was observed, the events were likely associated with the injection procedure itself.

3) Myositis. Two cases of myositis were reported as adverse events in the study. One case was coded as a severe event occurring the OLE-BSA phase (Table 32). This was an 11 y/o female patient, subject #1007, who developed CPK elevation up to 1055U/L (CTC grade 3 event; normal range 18-187U/L) on day 669 of the study. The patient had a previous history of muscle weakness, but no previous CPK elevation was reported. The study treatment was withheld and the CPK subsequently normalized. The patient was able to resume adalimumab treatment but had several sporadic CPK elevations that never exceeded CTC grade 2 level. The investigator considered CPK elevation and the reported "severe myositis" as possibly related to the study drug. The second case was coded as "myositis" and occurred in the OLE-FD phase in a 16 y/o American Indian /Alaskan Native male patient, subject # 1612. The CPK was elevated to 456U/L (CTC grade 2; normal range 18-198U/L). The subject had several other CPK elevations of a lesser degree throughout the study but was able to continue study treatment. The subject was also reported to have a few transient episodes of myoglobinuria and back pain which he apparently reported during the OLE-FD phase. The investigator considered CPK elevation related to the study treatment. The etiology of the myoglobinuria and back pain and their relatedness to CPK elevation was not determined.

Of the cases summarized above, a case of new onset seizure disorder while on adalimumab is concerning, since rare cases of new onset seizure disorder were reported with other TNF-blockers. A few syncopal episodes were likely related to injection administration. Two cases of severe CPK elevations may be related to the study treatment, although it is possible that there were other factors contributing to their presentations (previous h/o muscle weakness in the 11y/o girl and unclear concurrent history of myoglobinuria in the 16 y/o boy). Nonetheless, the elevation in CPK deserves further analysis and is presented in the section below.

Creatine phosphokinase (CPK) elevation

The following analysis of CPK elevations was conducted to explore the occurrence of CPK elevations while on study treatment. Table 33 shows shifts in CPK from normal to different levels of elevation. Cases of severe elevation $\geq$ CTC grade 3 are described separately.

Table 33. Elevation in CPK observed in study DE038.

	OL-LI		DB				OLE-BSA		OLE-FD	
	MTX+ ada N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N= 57	MTX + ada N=59	Ada N=47
CPK										
Remained within CTC grade 0 (≤ULN), N (%)	84(99)	72(84)	33(89)	35(92)	23(82)	25(83)	62(87)	47(82)	49(83)	40(85)
Shifted from CTC grade 0 to CTC grade 1, N (%)		12(15)	3(8)	3(8)	5(18)	5(17)	6 (8)	6(11)	6(10)	4(9)
Shifted from CTC grade 0 to CTC grade 2, N (%)	1(1)	1(1)	1(3)				1(1)	1(<2)	3(5)	1(2)
Shifted from CTC grade 0 CTC grade 3, N (%)							2(3)	2(4)		
Shifted from CTC grade 0 CTC grade 4, N (%)								1(<2)		

CTC Grade 0 is ≤ULN; CTC grade 1 is >ULN-=<2.5ULN; CTC grade 2 is >2.5ULN-=<5ULN; CTC grade 3 is >5ULN- =<10ULN; CTC grade 4 is >10ULN.

Table 33 shows that CPK remained normal in about ~82-85% patients treated with adalimumab monotherapy and in about ~83-99% patients treated with the combination of MTX and adalimumab in different phases throughout the study. More pronounced elevations in CPK (grade 3 and 4) were observed with longer duration of therapy in OLE-BSA. Brief summaries of these cases are presented below:

1. 17 y/o male subject developed moderate CPK elevations on several occasions during the study and peak CPK elevation to 1037U/L on day 862. The patient remained asymptomatic, but concurrent mild elevations of AST and creatinine were observed. Hypercalcemia of mild degree (Grade 2 by CTC on one occasion) was observed in this subject throughout the study. The CPK remained elevated for over 1 year, but subsequently normalized on day 1534. The patient was able to continue study participation until day 1534.
2. 11 y/o female subject had CPK elevation to 1055U/L during the OLE-BSA phase (see case summary above describing the cases of myositis). Sporadic elevations of calcium of mild degree were observed in this subject.
3. 10 y/o female subject developed CPK elevations on several occasions during the DB and OLE-BSA phases, which peaked at 1490U/L on study day 343. The patient remained asymptomatic, and the CPK subsequently normalized. The patient was not enrolled in the OLE-FD study.
4. 16 y/o female subject developed CPK elevations on several occasions during the OL-LI, DB, and OLE-BSA phases, which peaked at 1618 U/L on study day 638. No associated symptoms or laboratory abnormalities were observed. The CPK subsequently normalized and the subject was able to continue study participation into OLE-FD phase.
5. 11 y/o female patient developed CPK elevations on several occasions during the OL-LI and OLE-BSA phases, which peaked at 2095U/L (CTC grade 4) on study day 1233. Concurrent AST elevation to 80 U/L was observed, no associated AEs were reported.

The CPK normalized on the subsequent visit on day 1345 (~4 months later) which was the first visit in the OLE-FD phase. The patient was able to complete 16 weeks of the OLE-FD phase without further CPK elevation.

6. One additional subject (not shown in Table 33) developed CPK elevation at 1152 U/L (CTC grade 3) associated with concurrent mild AST elevation 115 days after the last dose in the OLE-FD phase. This subject had not had any previous elevations in CPK and his creatine phopsphokinase level remained elevated at the time this information was received (Oct 2007).

Overall, the data suggest that adalimumab therapy may be associated with elevation in creatine phophokinase in subjects with no previous history of CPK elevation. More than 10% of patients develop mild (<2.5ULN) elevations in CPK. In about 1-5% of cases CPK elevation reached 5-fold and several severe elevations in CPK (>5-fold- <10 fold) were also observed in the study. It appears that children with severe CPK elevations had had recurrent mild CPK changes prior to more severe elevations in CPK levels. All but one severely elevated CPK levels returned to normal, and the patients remained asymptomatic. One case of possible new onset myositis was observed in the 11 y/o female child. However, according to the Sponsor, this patient had a previous history of muscle weakness which suggests that the treatment with adalimumab did not trigger but rather unmasked the underlying condition. It is also possible that the condition progressed independently of the administered treatment.

Lack of associated clinical symptoms (except questionable transient myoglobinuria and muscle weakness described in the two cases above) and willingness of the patients to continue study participation likely reflect both patients' and investigators' perception that the product's benefit outweighed the risk associated with CPK elevation. However, when used in clinical practice, like with any other product, individual variations in risk/benefit will have to be taken into account when adalimumab treatment is administered. Taken together these data present a possible adverse effect of the therapy that deserves further mention in the product label.

Autoantibody formation

As a class, TNF blockers are known for their ability to trigger autoimmunity in some patients. The spectrum of autoimmune processes may include different constellations of laboratory abnormalities and clinical symptoms from asymptomatic appearances of autoantibodies in the serum to frank autoimmune syndromes. To examine the possibility of occurrence of autoimmune phenomena with adalimumab treatment, anti-dsDNA antibodies were measured in study participants at baseline and at the end of 16 weeks of treatment in the OL-LI phase and the study participants were monitored for clinical presentations consistent with autoimmune syndromes throughout all four phases of the study. The study protocol did not specify measurement of anti-dsDNA antibodies at other phases beyond the OL-LI, or measurement of other antibodies such as anti-nuclear antibodies (ANA) and anti-phospholipid antibodies at any time during the study. Table 34 below presents rates of seroconversion for anti-dsDNA antibodies in pediatric population in study DE038.

Table 34. Proportions of anti-dsDNA+ subjects at baseline and at the end of OL-LI phase of the study DE038

	Patients anti-dsDNA+ at baseline	Patients anti-dsDNA+ at the end of OL-LI
MTX	5/83 (6%)	8/83 (10%)
Non-MTX	9/86(10%)	15/86(17%)

Anti-dsDNA were measured by RIA and EIA, adult normal ranges were used as guide to interpretation of antibody positivity. For RIA, any value > 3.6 IU/ml was considered positive. For EIA, any value >30 IU/ml was considered positive.

As expected in the mixed JRA population, some subjects were anti-dsDNA positive at baseline prior to beginning of treatment (5/83-6% in the MTX stratum and 9/86-10% in the non-MTX stratum). Of those who were negative at baseline, 3/78 (4%) of subjects in the MTX stratum and 6/77 (8%) of subjects in the non-MTX stratum became newly anti-dsDNA positive at the end of 16 weeks of treatment. Since the study protocol did not specify to measure anti-dsDNA antibodies beyond the OL-LI phase, not all subjects had anti-dsDNA measured in the DB phase.

Of those who had anti-dsDNA measured, an additional 6 subjects (4 from the MTX stratum and 2 from the non-MTX stratum) became anti-dsDNA positive in the DB phase.

Taking into account those who did not have their anti-dsDNA measured in the DB phase (considering them as remaining anti-dsDNA negative), the rates of seroconversion in the OL-LI and DB phase were at least 7/78(9%) in those treated with combination of adalimumab and MTX and at least 8/77(10%) in those treated with adalimumab monotherapy after 48 weeks of treatment. None of the subjects developed an autoimmune syndrome.

This analysis gives a preliminary estimate of adalimumab's ability to induce anti-dsDNA antibodies. The analysis is limited because no data for antibody formation were consistently collected in the DB, OLE-BSA, and OLE-FD phases. No data on antinuclear (ANA) and anti-phospholipid antibodies were collected. That no autoimmune syndromes have been observed during the study is somewhat reassuring, and supports the previous observations from adult studies that frank autoimmune syndromes are rare with adalimumab treatment.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

An adverse event (AE) was defined as any untoward medical occurrence (unfavorable or unintended sign, including abnormal laboratory finding, symptom, or disease) temporally associated with the use of medicinal (investigational) product, whether or not the event was considered causally related to the use of the product. Treatment-emergent AEs were defined as events beginning on or after administration of study drug or pre-existing conditions that worsened on or after study drug administration. For subjects who discontinued from the study an event was considered a treatment-emergent AE if it occurred up to 70 days after the last dose of study drug. All subjects who received at least one dose of adalimumab (N = 171) during the OL-LI phase were included in the analysis of AE data.

Individual investigators monitored patients for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigators also assessed and recorded any AE in detail, including date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to the study drug, any known alternated etiology, final diagnosis, and any action taken. All AEs were followed to a satisfactory conclusion.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All AEs in study DE038 were summarized by medical Dictionary for Regulatory Activities (MedDRA) Versions 7.0 System Organ Class / Preferred Term classification for the OL-LI and DB phases and by MedDRA Version 9.0 for the OLE-BSA and OLE-FD phases. This categorization was appropriate and accepted by the Agency as an adequate system of categorization and coding of adverse events.

7.1.5.4 Common adverse event tables

No malignancies, opportunistic infections including TB, congestive heart failure, CNS demyelinating diseases or lupus like syndromes were observed during the study.

OL-LI phase: Table 35 summarizes the most frequent AEs occurring in ≥ 5% of subjects treated in either stratum. Upon initiation of adalimumab treatment, the most frequent AEs in both strata were injection site pain (22% in non-MTX stratum) and injection site reaction (18% in the MTX stratum). Upper respiratory infections occurred in 10% subjects treated with adalimumab monotherapy and in 7% subjects treated with the combination of MTX and adalimumab.

Table 35. OL-LI AEs in>=5% of subjects with either adalimumab or combination of adalimumab and MTX.

	OL-LI		Overall
	MTX+ Adalimumab N=85	Adalimumab N=86	N=171
AEs by preferred term, n (%)			
Injection site pain	13(15)	19(22)	32 (19)
Injection site reaction	15 (18)	12(14)	27(16)
Injection site burning	8 (9)	9(10)	17(10)
Upper respiratory infection	6 (7)	9(10)	15(9)
Headache	8(9)	8(9)	16(9)
Juvenile arthritis	2(2)	8(9)	10(6)
Viral infection	6(7)	7(8)	13(8)
Pharyngo-laryngeal pain	2(2)	7(8)	9(5)
Contusion	9 (16)	5(6)	14(8)
Rash	5(6)	5(6)	10(6)
Nasal congestion	3(4)	5(6)	8(5)
Lymphadenopathy	1(1)	5(6)	6(4)
Pain	1(1)	5(6)	6(4)
Hypersensitivity	6(7)	4(5)	10(6)
Gastroenteritis	3(4)	4(5)	7(4)
Arthralgia	4(5)	4(5)	8(5)
Arthropod bite	6(7)	4(5)	10(6)
Nausea	5(6)	4(5)	9(5)
Cough	5(6)	4(5)	9(5)
Excoriation	5(6)	3(3)	8(5)
Nasopharyngitis	6(7)	2(2)	8(5)
Injury	5(6)	2(2)	7(4)
Sinusitis	5(6)	1(1)	6(4)

Data obtained from Sponsor's Table 77, p 344 and Table 14.3_1.3.1.1, CSR.

DB phase: Upon continuation of adalimumab treatment in the DB phase, the most common AEs associated with adalimumab monotherapy were viral infections and upper respiratory tract infections occurring in 20% of the patients. Injection site pain and burning were next most frequent with adalimumab monotherapy, their rates exceeded those seen in the placebo group (injection site pain 17% vs 11%, injection site burning 13% vs 0). Of the rest of the listed events, ear pain occurred in a rate exceeding the rate of placebo or other treatments (10% vs 0), but the small number of cases limits the interpretation (Table 36).

In the combination treatment arm, injection site reactions and contusion were the most frequent events (18%), followed by viral infections (16%), nasopharyngitis (13%), and upper respiratory infections (13%). The rate of vomiting is 10%, likely owing to the effect of MTX.

Table 36. AEs that occurred in the DB phase in >=5% subjects* in any treatment group and exceeded the rate seen with placebo treatment. The descending order is in the adalimumab monotherapy group.

Preferred Term	MTX+ placebo N=37	MTX +adalimumab N=38	Placebo N=28	Adalimumab N=30
Viral infection	2(5)	6(16)	3(11)	6 (20)
Upper respiratory tract infection	4(11)	5(13)	5(18)	6 (20)
Injection site pain	6(16)	7(18)	3(11)	5 (17)
Injection site burning	2(5)	1(3)	0	4(13)
Injection site reaction	1(3)	7(18)	1(4)	3(10)
Excoriation	1(3)	4(10)	1(4)	3(10)
Ear pain	0	0	0	3(10)
Contusion	5(14)	7(18)	2(7)	2(7)
Rhinitis	0	3(8)	0	2(7)
Hypersensitivity	0	2(5)	0	2(7)
Arthralgia	0	2(5)	0	2(7)
Paronychia	0	1(3)	0	2(7)
Acne	0	1(3)	1(4)	2(7)
Rash	1(3)	1(3)	0	2(7)
Muscle strain	1(3)	0	1(4)	2(7)

Source Table 14.3_1.3.1.2
* the following AEs occurred in >=5% of subjects, but their rate was highest among subjects treated with placebo alone compared with the three other groups: pain, abdominal pain, headache, joint sprain, injury, influenza, arthropod bite, pain in extremity, erythema, and pruritis.

No new safety signals were observed in the OLE-BSA phase of the study (Table of the most common AEs in OLE-BSA is shown in APPENDIX C).

OLE-FD phase: Table 37 examines the rates of the most frequent AEs occurring in the OLE-FD phase. Consistently with common AEs reported in the previous phases, viral infections and upper respiratory infections are among the most common AEs reported with adalimumab treatment. More subjects whose adalimumab dose was increased experienced headaches and pyrexia (13% vs 4% and 6% vs 0). More events of injection site reaction and irritation also seemed to be observed more with adalimumab dose increase (Table 37). Overall, the most common AE profile in the OLE-FD phase was similar to that observed in other phases of the study and did not include any unexpected adverse events.

Table 37. AEs observed in >=2 subjects in OLE-FD phase, AEs ranked for the adalimumab increased dose group.

	MTX+adalimumab		Adalimumab alone		Overall	
Adalimumab dose change	**Same/ Decreased**	**Increased**	**Same/ Decreased**	**Increased**	**Same/ Decreased**	**Increased**
	N = 28	**N = 31**	**N = 25**	**N = 22**	**N = 53**	**N = 53**
Proportion of subjects with any Adverse Events (one or more), n(%)	23(82)	24(77)	17(68)	19(86)	40(75)	43(81)
Adverse Events by MedDRA Preferred Term, n(%)						
Headache	2(7)	0	0	7 (32)	2(4)	7(13)
Viral infection	2(7)	1 (3)	2 (8)	5 (23)	4(8)	6 (11)
Upper respiratory tract infection	3 (11)	1(3)	4 (16)	3 (14)	7(13)	4(8)
Arthritis	3(10)	1(3)	0	3(14)	3(6)	4(8)
Pyrexia	0	1 (3)	0	2 (9)	0	3 (6)
Rhinitis	1 (4)	1(3)	1(4)	2(9)	2(4)	3(6)
Sinusitis	1(4)	3(10)	1(4)	0	2(4)	3(6)
Ear infection	1(4)	3 (10)	1 (4)	0	2 (4)	3 (6)
Viral upper respiratory tract infection	0	2(6)	0	1(4)	0	3(6)
Injury	0	1 (3)	0	2 (9)	0	3 (6)
Acne	0	1(3)	0	2 (9)	0	3(6)
Injecton site irritation	0	2	0	2 (9)	0	2(4)
Injection site pain	1(4)	1(3)	0	1(4)	1(2)	2(4)
Injection site reaction	0	1(3)	0	1(4)	0	2(4)
Hypersensitivity	1(4)	0	0	2 (9)	1(2)	2(4)
Acute tonsillitis	0	2(6)	0	0	0	2(4)
Herpes Simplex	1(4)	2(6)	0	0	1(2)	2(4)
Nasopharyngitis	1(4)	2(6)	1(4)	0	2(4)	2(4)
Excoriation	0	0	0	2 (9)	0	2 (4)
Arthralgia	1(4)	0	3(12)	2(9)	4(8)	2(4)
Juvenile arthritis	1(4)	0	1(4)	1(4)	1(2)	2(4)
Dermatitis contact	0	1(3)	1(4)	1(4)	1(2)	2(4)

Data source: Sponsor's Tables 81; 82; 14.3_1.4.2.1 from the original submission, Table 13, Table 2.4_1.3.1 from 120-day safety update

None of the common adverse events observed in study DE038 were unexpected; all of them have been observed in previous trials of adalimumab, and/or postmarketing reports and are consistent with the major categories of events mentioned in the product label.

7.1.6 Less Common Adverse Events

Review of less common adverse events (APPENDIX D) revealed no additional safety signals.

Several children developed wart-like palmar and plantar lesions coded as "skin papillomas" (Table 38). The majority were recurrent lesions in children who had them prior to study enrollment. Since warts are generally considered of viral etiology, it is conceivable that some of the lesions could occur or re-occur due to possible decrease in host defenses against viral infections while on adalimumab treatment. However, because of the paucity of the observed cases and relatively common occurrence of warts in pediatric population, it is difficult to make any conclusions about the relatedness of wart occurrence to adalimumab treatment. Future observations in larger populations of children may be able to provide more information in this regard.

Table 38. Neoplastic disorders by MedDRA preferred term occurring with adalimumab treatment in children with JRA in study DE038.

	OL-LI		DB				OLE-BSA		OLE-FD	
	MTX+ ada N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N=57	MTX + ada N=59	Ada N=47
Neoplastic disorders by preferred term, n (%)										
Skin papilloma	0	1(1)	0	1(3)	2(7)	1(3)	2(3)	3(5)	1(2)	1+1*(4)

Source data: Tables 14.3_1.3.1.1-2, 14.3_1.4.1., and 14.3_1.4.2.1.from the original submission; Table 2.4_1.3.1 from the 120-day safety update

None of the less common AEs were unexpected and have been previously reported in clinical trials, literature, and/or postmarketing reportes with adalimumab treatment.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Blood and urine samples were obtained at the baseline visit prior to beginning of the study treatment and at subsequent study visits according to the pre-specified in the protocol schedule. The following laboratory tests were obtained:

Hematology: hematocrit, hemoglobin, red blood cells, white blood cells, neutrophils, bands, lymphocytes, monocytes, basophils, eosinophils, platelet count.

Biochemistry: blood urea nitrogen (BUN), creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase, sodium, potassium, calcium, inorganic phosphorus, uric acid, total cholesterol, total protein, glucose, triglycerides

(TG), albumin, lactate dehydrogenase (LDH), creatine phophokinase (CPK), chloride, bicarbonate.

Serology: serum pregnancy test, rheumatoid factor, C-reactive protein, anti-dsDNA, hepatitis B (HBsAg), hepatitis C (HCV Ab), serum immunoglobulin G (IgG).

Urinalysis: specific gravity, ketones, pH, protein, blood, glucose, microscopic examination.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Analyses for drug-control comparison and long-term analyses of changes in the laboratory data were performed for all four phases of the study on the total denominators of all subjects participating in the study.

7.1.7.3 Standard analyses and explorations of laboratory data

Analyses focused on the hematology and clinical chemistry laboratory values. Changes from baseline in all laboratory parameters were summarized with the means and standard deviations (SD). Analyses of shifts from normal to abnormal were also performed. Some of the laboratory parameters were graded according to Common Toxicity Criteria grading, refer to Section.. Changes in liver parameters were summarized and examined separately (section).

7.1.7.3.1 Analyses focused on measures of central tendency

Hematology parameters

Table 39 shows mean changes in the hematology parameters observed in the OL-LI and DB phases. Of the clinically significant observations, more pronounced decreases in the white blood cell counts, neutrophil counts, and platelet counts were observed in the adalimumab-treated groups compared to placebo-treated groups. All of these changes are currently listed in the adalimumab package insert and represent expected effects of the product. Of note, increases in white blood cell counts and thrombocytosis are known manifestations of inflammatory process; therefore, general mean decreases in these parameters also partially reflect the positive effects of adalimumab toward normalization of laboratory parameters associated with inflammation.

Table 39. Mean changes in hematology parameters in the OL-LI and DB phases.

	OL-LI		DB				OL-LI and DB			
	Mean changes from OL-LI baseline at Week 16		Mean changes from DB baseline at week 48				Mean changes from OL-LI baseline at week 48			
	MTX+ ada N=79	Ada N=71	MTX+ Placebo N=15	MTX +ada N=22	Placebo N=9	Ada N=14	MTX+ Placebo N=15	MTX +ada N=22	Placebo N=9	Ada N=14
Hemoglobin (g/L)										
Baseline	12	12	13.3	13.4	12.9	12.7	12.6	12.6	12	12
Change	0.8	0.3	-0.3	0.06	0.06	0.2	0.5	0.9	1	0.8
Hematocrit (%)										
Baseline	37	36	39	38	37*	37 **	37	37	35	36
Change	1.3	0.6	-1	0.3	-0.25	1	0.7	1	2	1.7
RBC ($x10^{12}$/L)										
Baseline	4.6	4.6	4.7	4.8	4.7	4.8	4.5	4.7	4.4	4.7
Change	0.11	0.06	-0.07	0	-0.03	0.03	0.1	0.05	0.2	0.1
WBC ($x10^9$/L)										
Baseline	8.9	8.5	8.2	7.3	8.8	9.3	8.5	8	8.5	10
Change	-0.7	-0.09	-0.8	0.12	-1	-1.4	-1.05	-0.55	-0.6	-2
Neutrophils ($x10^9$/L)										
Baseline	5.9	5.3	4.8	3.8	5.1	4.8	5.7	5.2	5.5	6.6
Change	-1.4	-0.6	-0.2	0.1	-0.4	-0.7	-1.1	-1.2	-0.7	-2.45
Lymphocytes ($x10^9$/L)										
Baseline	2.3	2.5	2.8	2.8	2.9	3.7	2.2	2.1	2.3	2.7
Change	0.64	0.44	-0.6	0.03	-0.5	-0.6	0.05	0.7	0.1	0.3
Monocytes ($x10^9$/L)										
Baseline	0.43	0.44	0.43	0.39	0.47	0.42	0.4	0.4	0.4	0.5
Change	-0.02	0	-0.04	-0.04	-0.04	0	-0.02	-0.03	0.01	-0.12
Eosinophils ($x10^9$/L)										
Baseline	0.18	0.2	0.17	0.21	0.23	0.27	0.2	0.2	0.2	0.2
Change	0.03	0.02	0.02	-0.01	0	-0.06	0.01	0.01	0.01	0.04
Basophils ($x10^9$/L)										
Baseline	0.05	0.06	0.05	0.05	0.05	0.08	0.05	0.06	0.05	0.07
Change	0	0	-0.01	0	0	-0.02	0	0	0	0
Platelets ($x10^9$/L)										
Baseline	387	418	336	336	314*	347	378	371	450	401
Change	-43	-57	17.5	-13	-6.5	-54	-25	-48	-143	-108

Data Source: Table 97, Table 14.3__4.1.1., Table 99, Table 14.3_4.1.3
* n=8
**n=13

To examine the long term effect of adalimumab on hematology parameters an analysis of changes occurring from baseline OL-LI phase to the end of OLE-BSA phase was done. The original analysis of long term safety of adalimumab treatment performed by the Sponsor is shown in the right part of Table 40 where groups are presented according to their DB phase

treatment assignment. To examine safety of long term treatment of 1) adalimumab monotherapy and 2) the combination of MTX and adalimumab, the Agency combined the data within each stratum; these data are presented in the left part of Table 40.

When examining the mean changes in the same hematology parameters in the OLE-BSA phase, the same trends of decreases in WBC, neutrophils and platelets were observed but the changes appeared to be less pronounced than at the beginning of therapy in the OL-LI and DB phases (Table 39). No clinically significant changes in other hematology parameters were observed (data not shown).

Table 40. Mean changes in hematology parameters in the OLE-BSA phase from OL-LI baseline to week 72 OLE-BSA phase.

	MTX+ adalimumab N=56	Adalimumab N=45	MTX+ Placebo N=26	MTX +adalimumab N=30	Placebo N=22	Adalimumab N=23
WBC ($x10^9$/L)						
Baseline	9.0	8.6	9.8	8.3	8.1	9.1
Change	-1.4	-1.4	-1.6	-1.2	-1	-1.7
Neutrophils ($x10^9$/L)						
Baseline	6.1	5.4	6.8	5.4	4.9	5.9
Change	-1.7	-1.4	-1.8	-1.6	-1	-1.7
Platelets ($x10^9$/L)						
Baseline	387	403	409	369	395	411
Change	-79	-83	-90	-70	-73	-90

Table 100, CSR; Table 14.3_4.1.1.

To further examine whether the increase in adalimumab dose and exposure had any effect on the hematology parameters in the OLE-FD phase, the mean changes from OL-LI baseline and from OLE-FD baseline were examined separately (Table 41). Data presented in Table 41 show that slightly more pronounced changes in the hematological parameters in subjects whose dose of adalimumab was increased were observed in comparison with the OL-LI baseline. However, when mean changes from OLE-FD baseline were examined, no trends or any clinically meaningful differences were observed in the groups where adalimumab dose was increased compared with those whose adalimumab dose remained stable or was decreased.

Table 41. Mean changes in hematology parameters in the OLE-FD phase (up to week 16).

	MTX+adalimumab		Adalimumab alone	
Adalimumab dose change	Same/Decr	Increased	Same/ Decr	Increased
WBC, ($x10^9$/L)	N = 27	N = 27	N = 21	N =19
Group mean at OL-LI baseline	8.4	9.4	8.1	8.8
Change from OL-LI baseline to OLE-FD baseline	-1.1	-2.1	-1.3	-1.6
Group mean at OL-LI phase (%)	8.3	9.3	8.3	9.2
Change from OL-LI baseline to Final visit	-0.3	-1.5	-1.3	-1.6
Change from OLE-FD baseline to Final visit	0.9	0.6	0.1	0.1
Neutrophils, ($x10^9$/L)	N = 27	N = 27	N = 21	N =19
Group mean at OL-LI baseline	5.3	6.7	5.0	5.5
Change from OL-LI baseline to OLE-FD baseline	-1.3	-2.5	-1.2	-1.6
Group mean at OL-LI baseline	5.3	6.4	5.2	5.8
Change from OL-LI baseline to Final visit	-0.7	-1.9	-0.9	-1.7
Change from OLE-FD baseline to Final visit	0.7	0.4	0.6	-0.01
Platelet, s($x10^9$/L)	N = 26	N = 27	N = 21	N =19
Group mean at OL-LI baseline	359	409	366	465
Change from OL-LI baseline to OLE-FD baseline	-39	-95	-69	-136
Group mean at OL-LI phase (%)	353	409	368	465
Change from OL-LI baseline to Final visit	-48	-111	-91	-150
Change from OLE-FD baseline to Final visit	-6	-19	-19	6

Source Tables 14.3_4.1.2.1, CSR; Table 2.5_1.1 120-day safety update.
Includes only subjects with available labs OLE-FD

No clinically meaningful changes in the hemoglobin, hematocrit, RBC, monocytes, eosinophils, basophils, or lymphocytes were observed with dose increase in the OLE-FD phase (data not shown). Additional data covering changes in the hematological parameters up to week 48 OLE-FD phase were requested by the Agency and submitted by the Sponsor in the IR response on Oct 31, 2007 (Tables 4_1.1; 4_1.2). Review of these data did not reveal any additional safety signals.

Chemistry parameters

Analysis of mean changes in chemistry parameters was performed in a way similar to the analysis of hematology parameters as above. Changes in all chemistry parameters were reviewed. The same strategy of combining data into two strata in the OLE-BSA phase (as above for hematology parameters, Table) was applied to the analysis of mean changes in all chemistry parameters with long term treatment. No clinically meaningful changes were observed in the analysis of mean changes in all measured chemistry parameters in the OL-LI, DB, or OLE-BSA phases (appendix B). No clinically meaningful changes in the chemistry parameters were seen with increase in adalimumab dose in the OLE-FD phase up to week 48 (data not shown, Sponsor's tables 1_2.1, 1_2.2, 4_2.1, 4_2.2 from response to Information request, Oct 31, 2007).

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

To further explore any clinically meaningful changes that occurred in individual subjects, shifts from normal to abnormal ("high" defined as higher than the upper limit of normal or "low" defined as lower than the lower limit of normal) in both hematology and chemistry parameters were examined in all phases of the study. Table shows the proportions of subjects whose hematology parameters changed from normal to low at any time during the study.

Table 42. Laboratory hematology parameters that changed from normal to low at any time during the study.

	OL-LI at 16 week		DB from DB baseline (week 16) to DB final (week 48)				OLE-BSA phase From OL-LI baseline to any time during the OLE-BSA		From OL-LI to any time during the OLE-FD up to week 48			
Laboratory parameters	MTX+ ada N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N=57	MTX + ada N=59		Ada N=47	
									Same/ dec dose	Inc dose	Same/ Dec dose	Inc dose
Hematocrit	3 (4)	4(5)	4 (11)	2 (5)	5 (18)	3(10)	4(6)	10(18)	2/24(8)	1/22(4)	0	4/19(21)
Hemoglobin	3 (4)	4(5)	4 (11)	0	2 (7)	6(20)	6(8)	12(21)	3/27(18)	3/31(13)	3/24(21)	4/20(20)
RBC count	2 (2)	3(4)	1 (3)	1 (3)	0	0	6(8)	5(9)	1/25(4)	1/29(3)	0	3/20(15)
WBC count	0	1(1)	2 (5)	2 (5)	0	2 (7)	13(18)	7(12)	2/27(7)	2/30(7)	3/23(13)	2/20(10)
Neutrophils	1 (1)	1(1)	0	1 (3)	0	0	9/59(15)	2/50(4)	2/27(7)	2/31(6)	2/24(8)	1/20(5)
Lymphocytes	1 (1)	0	0	0	0	0	2(3)	0	0	0	0	1/21(5)
Monocytes	0	0	0	0	0	0	6(8)	2(4)	0	0	0	0

Tables 107, 109, 110, 111.
Source Table 14.3_4.4.1.1, CSR; 120-day safety update

As can be seen, decreases in hemoglobin were observed in up to ~20% of subjects treated with adalimumab monotherapy in the DB and OLE-BSA phase and in up to 8% of subjects treated with combination of MTX and adalimumab in the OLE-BSA phase. Some of these abnormalities are likely related to underlying anemia that is a manifestation of JRA and not necessarily to a drug effect. Decreases in WBC counts and neutrophils appear to occur slightly more frequently with long term treatment in the MTX stratum. The vast majority of the changes in hematology parameters were mild and some were moderate in severity, except the uncommon severe events discussed elsewhere in this review (Section 7.1.2). Decreases in hemoglobin, hematocrit, WBCs, and neutrophils are known effects of adalimumab and currently indicated in the product label. Of note, while no shifts from normal to low occurred in platelet counts, the mean changes showed overall decrease in platelets in subjects treated with adalimumab. It is likely that these decreases represent positive effect of adalimumab on the known manifestation of inflammation – thrombocytosis.

When shift changes from normal to high in hematology parameters were examined, no additional safety signals were identified.

Table 43 shows the proportions of subjects with shifts in chemistry parameters from normal or low to high that occurred at any time during the study. The most frequent laboratory abnormalities occurring in the study subjects appeared to be hypercalcemia, hypertriglyceridemia, increases in liver transaminases and increases in creatine phosphokinase. Upon further clarification with the Sponsor (Information Request, Oct 31, 2007) it was identified that measurements of glucose and lipids including triglycerides were not performed under fasting conditions; therefore, the data on any of these parameters including triglyceride elevations could not be interpreted from the aspect of drug effect since postprandial variability in the levels would be the most obvious explanation to the observed elevations. Analyses of elevations in creatine phosphokinase and liver transaminases are presented in Sections 7.1.3 and 7.1.7.5 respectively. Elevations in calcium in all but one cases were mild $\leq$ Grade 1 by CTC criteria and did not represent clinically significant or meaningful changes. In one subject (#702), hypercalcemia reached grade 2 level by CTC criteria without associated symptoms; this same subject had recurrent elevations in CPK (refer to Section 7.1.3 for more details).

Table 43. Change from normal/low (for OLE-BSA) to high at any time during the OLE-BSA and FD phases up to week 48.

	OL-LI		DB				OLE-BSA		FD			
			MTX		Non-MTX				MTX+adalimumab		Adalimumab	
Laboratory parameters N (%)	MTX+ ada N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N=57	Same/ dec dose	Inc dose	Same/ Dec dose	Inc dose
Chloride	1 (1)	0	0	0	1 (4)	0	1(1)	3(5)	0	0	0	0
Glucose	4 (5)	2 (2)	3 (8)	2 (5)	1 (4)	0	11(16)	7(13)	3/26(12)	3/29(10)	3/24(12)	1/19(5)
Potassium	0	0	0	0	0	0	1(1)	0	0	0	0	0
Sodium	1 (1)	0	2 (5)	0	0	1 (3)	4(6)	6(10)	0	1/30(3)	0	0
BUN	2 (2)	0	0	0	0	1 (3)	3(4)	1/55(2)	1/27(4)	0	0	0
Creatinine	0	0	0	0	0	0	3(4)	3(5)	0	2/31(6)	1/25(4)	1/20(5)
Albumin	8 (9)	13 (15)	3 (8)	3 (8)	3 (11)	5 (17)	14(21)	17(31)	3/23(13)	5/31(16)	3/23(13)	2/20(10)
Calcium	4 (5)	8 (9)	2 (5)	2 (5)	1 (4)	2 (7)	18/58(31)	18/54(33)	3/21(14)	7/26(27)	4/23(17)	4/19(21)
Inorganic Phosphorus	3 (4)	2 (2)	0	0	2 (7)	1 (3)	6(9)	1(2)	1/27(4)	2/31(6)	0	1/20(5)
Total Protein	3 (4)	3 (4)	2 (5)	0	0	0	6(9)	11/54(20)	1/26(4)	1/28(4)	0	1/18(6)
Uric Acid	3 (4)	5 (6)	1 (3)	1 (3)	1 (4)	1 (3)	6(9)	5(9)	0	0	0	1/20(5)
Total Cholesterol	3 (4)	3 (4)	1 (3)	1 (3)	1 (4)	0	5(7)	2/53(4)	2/27(7)	0	1/23(4)	0
Triglycerides	12(14)	8 (9)	3 (8)	6(16)	4 (14)	4(13)	27/54(50)	25/42(60)	9/23(39)	6/21(29)	3/16(19)	6/16(38)
LDH	1 (1)	1 (1)	0	1 (3)	0	0	5/68(7)	4/56 (7)	1/27(4)	2/28(7)	0	0
ALT	9 (11)	3 (4)	0	2 (5)	2 (7)	1 (3)	15/68(22)	9/55(16)	1/26(4)	6/29(21)	2/23(9)	2/20(10)
AST	6 (7)	1 (1)	0	1 (3)	0	1 (3)	14/69(20)	5(9)	1/27(4)	3/30(10)	1/25(4)	2/20(10)
Total Bilirubin	1 (1)	0	0	0	0	0	3(4)	2(4)	1/27(4)	1/31(3)	0	1/20(5)
Bicarbonate	0	0	0	0	0	0	1(1)	1(1)	0	0	0	1/20(5)
GGT	0	1 (1)	0	1 (3)	1 (4)	0	2/70 (3)	1/56(2)	0	1/30(3)	0	0
CPK	1 (1)	13 (15)	4(11)	3(8)	5(18)	5(17)	9(13)	10(18)	5/27(18)	4/31(13)	4/25(16)	1/20(5)

Data obtained from Tables 112-116, CSR; 120-day safety update, IR response from Oct 31, 2007.

No additional safety signals were identified upon review of shifts from normal to low in the chemistry parameters.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

When outlier values (>=Grade 3 events) for laboratory parameters were examined in the OL-LI and DB phases, no additional safety signals were observed. There were several cases of lymphopenia, neutropenia and decreased hemoglobin, of which combination of lymphopenia and neutropenia led to drug discontinuation in one patient with previous history of recurrent leucopenia (Section 7.1.2). Isolated events of electrolyte elevations (hypernatremia, hyperkalemia) as well as a single case of hyperglycemia were not related to study treatment.

Table 44 shows occurrence of Grade>= 2 events in the OLE-BSA and OLE-FD phases. No new safety signals could be identified.

Table 44. Grade >=2 events occurred in the OLE-BSA and OLE-FD phases.

	OLE-BSA, n=128		OLE-FD (up to week 48), n=106	
	Transient (1 occasion) N(%)	Recurrent (2 or more occasions) N(%)	Transient (1 occasion) N(%)	Recurrent (2 or more occasions) N(%)
Decrease in Hb	1(1)	3(2)	2(2)	1(1)
Leucopenia	5(4)	2(2)	4(4)	1(1)
Neutropenia	1(1)	0	0	0
CPK	6(5)	1(1)	4(4)	0
Hyperglycemia	0	1(1)	0	1(1)

Data obtained from Sponsor's Table 1; 1_2.1; 1_2.2 from IR response submitted November 6, 2007

7.1.7.4 Additional analyses and explorations

Refer to Section 7.1.3 for analysis of creatine phosphokinase elevations.

7.1.7.5 Special assessments

An analysis investigating changes in liver function tests was performed to assess the LFT changes while on treatment with adalimumab (Table 45). Throughout the study, elevations in ALT were more common than those of AST. Liver changes were more frequent in the MTX stratum in each phase of the study, likely owing to the known effects of MTX on the liver.

In the OL-LI phase, 4 subjects developed concomitant elevations of both ALT and AST, one subject was discontinued from the study for LFT elevation (#5302, refer to Section 7.1.3 for details on study dropouts). None of the subjects had concurrent elevation in transaminases and bilirubin. The LFTs returned to normal during the study in all subjects except subject #5302 whose LFTs returned to normal after discontinuation of the study treatment.

In the DB phase, there were five reports of concomitant transaminase elevations (3 in placebo group, two in adalimumab group). All subjects including the subject with an isolated bilirubin increase remained asymptomatic.

In the OLE-BSA phase, more subjects in the MTX stratum had LFTs changes compared to the non-MTX stratum. One subject had concomitant elevation in ALT (>8UNL) and AST (<3ULN). MTX was discontinued is this subject while treatment with adalimumab was not interrupted. Subsequently, LFTs returned to normal levels in four weeks after discontinuation of MTX. Of note, in the OLE-FD phase (up to 16 weeks), 3 subjects had mild elevations in LFTs; all of these subjects had the adalimumab dose increased in the OLE-FD phase.

Table 45. Shifts from normal to abnormal in liver function tests in all phases of the study.

	OL-LI		DB				OLE-BSA		OLE-FD up to week 16	
	MTX+ ada N=85	Ada N=86	MTX+ Placebo N=37	MTX +ada N=38	Placebo N=28	Ada N=30	MTX +ada N=71	Ada N=57	MTX + ada N=59[2]	Ada N=47[3]
ALT										
Remained within <1.5ULN	73(86)	82(95)	32(86)	32(85)	26(93)	29 (97)	62(87)	55(96)	51(86)[1]	41(87)
Shifted from <1.5ULN to >=1.5ULN-<3ULN	8(9)	3(4)	3(8)	4(10)	2(7)	1(3)	5(7)	1(2)	1(2)*	1(2)*
Shifted from <1.5ULN to >=3ULN-<5ULN	3(4)			2(5)			2(3)	1(2)		
Shifted from <1.5ULN to >=8ULN							1(1)			
Remained within >=1.5ULN-<3ULN		1(1)	1(3)				1(1)			
Shifted from >=1.5ULN-<3ULN to >=3ULN-<5ULN	1(1)		1(3)							
AST										
Remained within <1.5ULN	79(93)	85(99)	34(92)	36(94)	28(100)	30 (100)	65(91)	55(96)	52(88)	41(87)
Shifted from <1.5ULN to >=1.5ULN-<3ULN	5(6)		3(8)	1(3)			4(6)	2(4)		1(2)*
Shifted from <1.5ULN to >=3ULN-<5ULN	1(1)			1(3)			2(3)			
Remained within >=1.5ULN-<3ULN		1(1)								
Total bilirubin										
Remained within <1.5ULN	82(96)	86(100)	36(97)	37(97)	28(100)	30 (100)	71 (100)	57 (100)	52(88)	42(89)
Shifted from <1.5ULN to >=1.5ULN-<3ULN	3(4)			1(3)						
Remained within >=1.5ULN-<3ULN			1(3)							

[1] Includes one subject who started with ALT value of >=1.5-3XULN and shifted to <1.5ULN
[2] Data on seven subjects from same/decreased dose group are not reported/unknown
[3] Data on four subjects from same/decreased dose group and on one subject from increased group are not reported / unknown.
*increased dose adalimumab group
Source 14.3_4.10.3.1

Overall, increases in LFTs were transient and primarily of mild or moderate degree; they occurred more frequently in the MTX stratum. Elevations in LFTs were also seen with adalimumab monotherapy, regardless of concomitant MTX administration. No cases of concurrent elevation of transaminases and bilirubun were observed. Two severe cases of LFTs elevations occurred in the MTX stratum. Adalimumab was discontinued in one case and MTX was discontinued in the other case; LFTs normalized in both subjects. It is recommended that a statement be added to the ADVERSE REACTIONS section of the product label to inform the

treating physicians about the possible abnormal laboratory findings of elevated ALT, AST, [redacted] in children treated with adalimumab with or without MTX.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured in children throughout all four phases of the study.

7.1.8.2 Standard analyses and explorations of vital signs data

7.1.8.2.1 Analyses focused on measures of central tendencies

Table 46 shows mean changes in the vital signs (VS) at different time points at OL-LI and DB phases in study DE038. No clinically meaningful changes in vital signs occurred in the study (data from OLE-BSA and OLE-FD phases reviewed but not shown), except the observation of a small trend toward an increase in systolic blood pressure in children treated with adalimumab monotherapy and in those whose dose of adalimumab was increased in the OLE-FD phase (Tables 46-48).

Table 46. Mean changes in vital signs in the OL-LI phase and in children who completed DB phase.

	OL-LI – change at week 16		DB- change at week 48			
	MTX+ ada N=81	Ada N=77	MTX+ Placebo N=15	MTX +ada N=24	Placebo N=9	Ada N=17
Systolic BP						
Baseline Mean[1]	109	106	107	110	110	101
Mean (Median) change	0.04(1)	1.2(1)	-0.3(0)	-0.8(-1)	-0.3(2)	5(6)
Diastolic BP						
Baseline Mean	66	63	63	66	63	62
Mean (Median) change	-1.9(0)	-1.2(0)	5(5)	-2(-1)	0.8(2)	0.06(0)
Pulse						
Baseline Mean	89	87	87	89	87	89
Mean (Median) change	-5(-4)	-4(-4)	-2(0)	-7(-7)	-2.6(-4)	-4(-6)
Temperature(C)						
Baseline Mean	36.6	36.5	36.7	36.4	36.5	36.4
Mean (Median) change	-0.1(0.1)	0.1(0)	-0.5(0.3)	-0.06(0.05)	0.1(0.1)	-0.1(0)

[1] baseline mean at OL-LI is based on the available data in each phase
Source Tables: 14.3_5.1.1; 14.3_5.1.2

Table 47. Mean changes in vital signs in the OLE-BSA phase at week 72.

	OLE-BSA according to two strata. Change to week 72		OLE-BSA according to DB phase assignment Change to week 72			
	MTX+ ada N=58	Ada N=46	MTX+ Placebo N=27	MTX +ada N=31	Placebo N=22	Ada N=24
Systolic BP (mmHg)						
Baseline Mean	110	108	112	108	109	107
Mean (Median) change	-0.4 (0)	0.7 (-1)	0.3(0)	-1(0)	-2(-2)	3(-0.5)

Source Table: 14.3_5.1

Table 48. Mean changes in the OLE-FD phase up to week 16.

	OL-LI baseline to OLE-FD final visit at week 16			
	MTX +adalimumab		adalimumab	
	Same/ decreased dose N=23	Increased dose N=31	Same/ decreased dose N=21	Increased dose N=21
Systolic BP				
Baseline Mean	112	105	109	105
Mean (Median) change	-0.7(-2)	0.8(3)	-0.7(0)	0.8(5)

Source Table: 14.3_5.2.1

Review of additional VS data up to week 48 in the OLE-FD phase revealed no additional safety signals (Tables 4_3.1; 4_3.2; 4_4.1; 4_4.2 from response to Information request Oct 31, 2007).

7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal

To further explore the changes in BP observed in study DE038 the Agency requested the Sponsor categorize the children with BP values meeting criteria for HTN and pre-HTN according to the Fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents[2].

In this post-hoc analysis (Table 49) hypertension was defined by the Sponsor as three separate (not necessarily consecutive) instances of a SBP and/or DBP $\geq$ 95th percentile at any time during the study. Pre-hypertension was defined as any instance of a SBP or DBP between 90-94th percentile at any time during the study or any visit reading where SBP >= 120mmHg and DBP >=80 mmHg. As pointed out by the Sponsor, this post-hoc analysis was limited since the vital signs measurements were not taken under the same controlled conditions as they would be in a hypertension trial and may have been affected by variability in measuring techniques at different study sites. The within visit readings were not averaged as required per the guidelines. Moreover, the subjects were aware that they would receive an injection during the visit, and the associated anxiety could also influence the BP results during this study.

Additionally, the subject population consisted of children who had other risk factors potentially predisposing to BP elevation, namely: chronic steroid treatment that often leads to metabolic perturbations and truncal obesity, sedentary lifestyle due to chronic disease, chronic treatment with non-steroidal anti-inflammatory medications. Finally, for the majority of children, duration of study participation was approximately 3 years and certain proportion of accidental isolated high BP readings in the uncontrolled conditions could be attributed to chance.

Table 49. Proportion of subjects meeting criteria for HTN and pre-HTN during the study according to the post-hoc analysis

PRE-DOSE	POST-DOSE			
	HTN	Pre-HTN	Normal BP	Total
HTN	26/45(58%)	12/71(17%)	2/54 (4%)	40
Pre-HTN	5/45(11%)	9/71(13%)	4/54(7%)	18
Normal BP	14/45 (31%)	50/71(70%)	48/54(89%)	112
Total	45/170 (26.5%)	71/170 (42%)	54/170 (32%)	170

Data from Sponsor's Table 4, IR from Oct 31, 2007. All subjects had at least one pre-dose and one post-dose visit.
Pre-Dose = the worst value prior to the first open-label lead-in dose.
Hypertensive = SBP and/or DBP $\geq$ 95th percentile on more than 3 post-Baseline visits.
Pre-hypertensive = [SBP or DBP $\geq$ 90th percentile to < 95th percentile] OR [any visit reading where SBP $\geq$ 120 mmHg and DBP $\geq$ 80 mmHg].

To delineate the occurrence of persistent BP elevation, an additional analysis of BP elevations to HTN or pre-HTN ranges on $\geq$ 3 consecutive visits was performed by this reviewer.

According to the analysis performed by the Sponsor (Table 49), 26/170 (15%) children had their systolic or diastolic BP elevated $\geq$ 95-th percentile at least one time before the beginning of treatment and $\geq$ 3 times (not always consecutive visits) at any time during their respective duration of study participation. Of those, 21/170 had SBP and or DBP elevated $\geq$ 95-th percentile on *three or more consecutive visits* at any time during the study. Thus, considering the criteria and the quality of BP measurements in the study, ~12% of children entered the study DE038 with BP elevated $\geq$ 95 percentile and had BP elevation in the range of HTN[2] on three or more consecutive visits during the study.

Fourteen out of 170 subjects with available data had normal BP during the first two pre-treatment visits and had SBP or DBP $\geq$ 95-th percentile on three or more visits (not always consecutive) at any time during their respective durations of study participation (Table 49). Of those, 3/170 or 2% of subjects (two subjects treated with adalimumab and one subject treated with placebo in the DB phase) had SBP and or DBP elevated $\geq$ 95-th percentile on three or more consecutive visits at any time during the study and an additional 3/170 or 2% of subjects (two subjects treated with adalimumab and one subject treated with placebo in the DB phase) had their SBP elevated $\geq 90^{th}$ percentile on three or more consecutive visits. Thus, in addition to 21/170 (12%) subjects with persistent BP elevation at baseline and during the study, 6/170 (4%) more subjects who were normotensive at baseline developed persistent BP elevation $\geq$ 90-th

percentile on three or more consecutive visits. Of note, all of these six subjects were treated with NSAIDs and prednisone during the study. None of the children with newly observed elevations in blood pressure required any antihypertensive treatment.

Three out of five subjects with BP elevated in the pre-HTN range at baseline ($\geq 90^{th}$ percentile) had persistent BP elevation on 3 or more consecutive visits during the study.

Taken together these data could be interpreted as follows:

1. The baseline incidence of persistent BP elevation (some with known diagnosis of hypertension) was about 12% in a population of children with poly-articular JRA with previous or concurrent history of treatment with chronic steroids, NSAIDs, less active lifestyle due to chronic disease.
2. An additional 6/170 or 4% of children developed persistent elevation in BP $\geq$ 90th percentile (2% $\geq$ 95 percentile) of their respective age and gender distributions while on study treatment. Although 4/6 children were treated with adalimumab and 2/6 were treated with placebo in the DB phase of the study, the interpretation of these numbers is extremely limited due to the small number of patients and universal exposure of all study participants to adalimumab.
3. It is conceivable that the occurrence of 4% of children developing persistent BP elevation over the period of the study reflects influence of other factors and not necessarily the study treatment. However, considering all the limitations indicated above, a small increase in occurrence of HTN in children may be consistent with findings in adult RA studies where HTN was reported in 5% of adults treated with adalimumab compared to 3% of those treated with placebo (Source: Humira® label).

[redacted]

7.1.10 Immunogenicity

In adult studies, adalimumab demonstrated the potential to trigger development of anti-adalimumab antibodies in certain individuals. Therefore, it was particularly important to assess the immunogenic potential of adalimumab in children with JRA in study DE038. The Sponsor defined anti-adalimumab antibody (AAA) positivity as AAA concentration greater than 20 ng/mL and the signal not be reduced by >=50% after addition of 10% human serum. Subjects were considered AAA-positive (AAA+) if the positive signal was observed within 30 days following the subject's last adalimumab dose. AAA status was measured in subjects in OL-LI, DB, and OLE-FD phases of the study. The Sponsor did not measure AAA-status during the OLE-BSA phase which limits assessment of immunogenicity upon re-challenge with this biological product.

OL-LI and DB phases:

During the OL-LI and the DB phases of the study 27/171 (16%) subjects had at least one AAA+ sample while on treatment. Of those, nineteen subjects became AAA+ during the OL-LI phase: 15/86-17% subjects treated with adalimumab alone and 4/85(5%) subjects treated with the combination of adalimumab and MTX (see Table below). Additionally, in the DB phase, 1/38 (3%) subjects treated with combination of MTX and adalimumab and 7/30 (23%) subjects treated with adalimumab alone developed AAA, compared to no new subjects showing AAA-positivity among those treated with placebo or MTX alone. Overall, among children with JRA treated with the combination of MTX and adalimumab the rate of AAA+ was 6% (5/85); and among those treated with adalimumab alone the rate was 26% (22/86). These immunogenicity rates exceed the rates observed in adult studies: 12% with adalimumab monotherapy and 1% with adadlimumab and concomitant MTX treatment.

These data suggest that adalimumab is particularly immunogenic in children when given as monotherapy; this observation is consistent with the adult data.

Effect on serum concentrations of adalimumab:

In the OL-LI phase, serum concentrations of adalimumab in subjects who became AAA+ started to decline between weeks 2 and 4 and then gradually reached negligible levels, compared to AAA- subjects, whose serum concentrations of adalimumab gradually increased to week 16. In the DB phase, serum concentrations of adalimumab remained constant in AAA- subjects and declined to negligible levels in AAA+ subjects, thus suggesting that AAA increased the clearance of adalimumab.

Effect on efficacy:

It is important to note that only 2/4 AAA+ subjects from MTX stratum and 6/15 AAA+ subjects from the non-MTX stratum got randomized into DB phase. During the DB phase, none of the 16 AAA+ subjects discontinued from the study.

Table 50. Proportions of PedACR 30 responders in the OL-LI phase by AAA status.

PedACR30 Responders Open-Label Phase N (%)						
Open-Label AAA Group	**N**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**
All (AAA-)	152	88 (58%)	112 (74%)	123 (81%)	133 (88%)	132 (87%)
All (AAA+)	19	15 (79%)	14 (74%)	11 (58%)	9 (47%)	12 (63%)
MTX (AAA-)	81	42 (52%)	59 (73%)	72 (89%)	73 (90%)	76 (94%)
MTX (AAA+)	4	4 (100%)	4 (100%)	2 (50%)	2 (50%)	4 (100%)
w/o MTX (AAA-)	71	46 (65%)	53 (75%)	51 (72%)	60 (84%)	56 (79%)
w/o MTX (AAA+)	15	11 (73%)	10 (67%)	9 (60%)	7 (47%)	8 (53%)

Data from Sponsor's Table 11, R&D/05/763

Table 50 shows that in the OL-LI phase, the PedACR 30 response rate has gradually decreased with time and was overall lower among AAA+ subjects compared with AAA- subjects. Although the lowest response was observed among AAA+ subjects treated with adalimumab alone (53%), half of the subjects still remained PedACR 30 responders.

Consistently with the above, in the DB phase, the response rate in the adalimumab arm among AAA+ subjects declined to 42% by week 48 compared with a less pronounced decline in response rate among AAA- subjects (67% by week 48).

Effect on safety:

In the OL-LI phase, AEs occurred in all AAA+ subjects in both strata compared to ~80% rate in AAA- subjects (Table 51). The most frequently occurring events were infections, injection site reactions and immunologic reactions. In the non-MTX stratum, review of the overall profile of infectious complications among the AAA+ subjects did not reveal any additional signals. Of note, herpetic infections occurred in both AAA+ and AAA- subjects. Immunologic reactions consisted of hypersensitivity reactions, drug hypersensitivity and seasonal allergies and occurred more frequently among AAA+ subjects treated with adalimumab alone. No serious immunologic reactions occurred at any time during the study.

Table 51. Proportion of subjects with AEs in OL-LI phase in all subjects according to their AAA+ status

	MTX stratum, n (%)		Non-MTX stratum, n(%)	
	AAA+	**AAA-**	**AAA+**	**AAA-**
	N = 4	**N = 81**	**N = 15**	**N = 71**
Adverse Event (AE)	4 (100)	70 (86)	15 (100)	56 (79)
Infectious AE	0	37 (46)	6 (40)	33 (46)
Injection Site Reaction Related AE	2 (50)	33 (41)	6 (40)	31 (44)
AE of Immunologic Reaction	0	7 (9)	3 (20)	2 (3)

Data from Tables 15.5_7.1-2 (R&D/05/763)

In the DB phase, in the non-MTX stratum, the profile of infectious complications was similar between AAA+ and AAA-subjects. A case of H. simplex was again noticed among AAA+ population. A few hypersensitivity reactions occurred among both AAA+ and AAA- subjects (Table 52).

Table 52. Proportion of subjects with AEs in DB phase in all subjects according to their AAA+ status.

	Double-Blind MTX stratum, N (%)				Double-Blind non- MTX stratum, N (%)			
	AAA+		AAA-		AAA+		AAA-	
	Placebo	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab
	N = 1	N = 2	N = 36	N = 36	N = 1	N = 12	N = 27	N = 18
Adverse Event (AE)	0	1 (50)	27 (75)	31 (86)	1 (100)	12 (100)	20 (74)	16 (89)
Infectious AE	0	0	19 (53)	22 (61)	0	8 (67)	11 (41)	11 (61)
Serious Infectious AE	0	0	0	1 (3)	0	1 (8)	0	0
Inj Site Reaction Related AE	0	1 (50)	9 (25)	13 (36)	0	3 (25)	4 (15)	8 (44)
AE of Immunologic Reaction	0	0	0 (0%)	2 (6)	0	1 (8)	0	2 (11)

Data from 15.5_7.3-4 (R&D/05/763)

Overall, there was no particular pattern in occurrence of AEs among AAA+ subjects compared with AAA- subjects.

OLE-FD phase:

Of the 106 subjects who entered the OLE-FD phase, 17 subjects were found AAA+ at least once during the study. Of those, 14/17 subjects were found positive during the OL-LI and the DB phases of the study and 3/17 were found positive at the OLE-FD baseline prior to receiving the first dose in the OLE-FD phase (Data from Table 15, 15.5_1, R&D/06/577).

By week 16, four subjects discontinued the study prematurely; 2 out of those 4 were AAA+ subjects from the non-MTX stratum.

Table 53 shows adverse events grouped by system organ class in the MedDRA terminology in the OLE-FD phase.

Table 53. Adverse events grouped according to system organ class in MedDRA system in the OLE-FD phase among AAA+ and AAA- subjects.

	MTX		Non-MTX	
System Organ Class	**AAA + (N = 5)**	**AAA - (N = 54)**	**AAA + (N = 12)**	**AAA - (N = 35)**
Any Adverse Event	4 (80%)	31 (57%)	10 (83%)	16 (46%)
Gastrointestinal Disorders	0	3 (6)	2 (17)	0
General Disorders and Administration Site Conditions	0	5 (9)	3 (25)	2 (6)
Immune System Disorders	0	0	2 (17)	0
Infections and Infestations	2 (4)	15 (28)	7 (58)	5 (14)
Injury, Poisoning and Procedural Complications	0	2 (4)	3 (25)	3 (9)
Musculoskeletal and Connective Tissue Disorders	1 (20)	5 (9)	3 (25)	3 (9)
Neoplasm's Benign, Malignant and Unspecified Skin Papilloma	0	0	1 (8)	0
Nervous System Disorders	0	1 (2)	1 (8)	3 (9)
Reproductive System and Breast Disorders	1 (20)	1 (2)	1 (8)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (20)	0	0	0
Skin and Subcutaneous Tissue Disorders	0	5 (9)	1 (8)	2 (6)

Data Source Table 20, Table 15.5_7, R&D/06/577

Overall, more subjects developed AEs among AAA+ compared to AAA- subjects (80-83% vs 46-57%) in the OLE-FD phase (Table 53). Of the immune system disorders two cases of non-serious hypersensitivity reactions occurred in the AAA+ subjects treated with adalimumab alone. No new signal was observed upon reviewing the profile of infectious complications in AAA+ and AAA- subjects in both strata. One case of skin papilloma was reported in AAA+ subects, unlikely related to study treatment. Review of the rest of the reported AEs did not reveal any safety signal in association with AAA+ status.

7.1.11 Human Carcinogenicity

No malignancies occurred in study DE038. However, malignancies, including lymphomas and non-melanoma skin cancers are known potential associations of anti-TNF treatment and are listed in the WARNINGS and ADVERSE REACTIONS sections of the current Humira ® package insert. Although no malignancies have been observed in this study, it is possible that some events will be observed post marketing (refer to Section 7.3 and Section 1.2.3 for recommendations on postmarketing studies).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal effects were observed in pediatric study DE038 and no withdrawal phenomena are anticipated with the use of adalimumab. Similarly, there is no evidence or expectation of patient abuse of adalimumab.

7.1.14 Human Reproduction and Pregnancy Data

Female subjects ≥ 10 y/o were required to have a negative pregnancy test at screening and at all subsequent visits. All sexually active males and females were requested to have a reliable method of contraception during the study. One pregnancy occurred in a 17 y/o female subject during the OLE-BSA phase; the patient chose to have an elective abortion (refer to Section). Two additional pregnancy occurrences were reported in the 120-day safety update (August 1 2006 and March 15, 2007): one pregnancy resulted in a spontaneous abortion and the other is ongoing.

7.1.15 Assessment of Effect on Growth

It is established and well known that growth disturbances are characteristic for children with JRA. Linear growth is usually retarded during periods of active disease. Growth and development were assessed at the baseline and at the end of each phase in study DE038 (Table 54). There were no developmental delays or loss of developmental milestones reported as adverse events during the study. Table 54 shows the observed mean changes in height and weight in children with JRA treated with adalimumab. Overall, increases in height and weight were observed in all treatment groups, numerically slightly higher in the groups receiving adalimumab treatment. Although limited in their interpretation, the data might be suggesting an overall positive effect on growth owing to less disease activity in children with JRA treated with adalimumab.

Table 54

A. Change in weight and height in the OL-LI phase and DB phase in children who completed the DB phase.

	OL-LI – change at week 16		DB- change at week 48			
	MTX+ ada N=81	Ada N=77	MTX+ Placebo N=15	MTX +ada N=24	Placebo N=9	Ada N=17
Height(cm)						
Baseline Mean	145	144	144	146	152	140
Mean (Median) change	1.4(1)	1.2(1)	5(5)	5(5)	3(2)	5(7)
Weight(kg)						
Baseline Mean	44	41	45	43	48	37
Mean (Median) change	1.6(2)	1.7(2)	1.6(3)	5(5)	5(4)	4(3)

B. Change in weight and height in the OLE-BSA phase.

	OLE-BSA according to two strata. Change to week 72		OLE-BSA according to DB phase assignment Change to week 72			
	MTX+ ada N=58	Ada N=46	MTX+ Placebo N=27	MTX +ada N=31	Placebo N=22	Ada N=24
Height(cm)						
Baseline Mean	144	147	144	144	148	146
Mean (Median) change	10 (10)	8 (8.5)	9(9)	10(12)	8(8)	9(10)
Weight(kg)						
Baseline Mean	44	44	45	44	46	43
Mean (Median) change	8 (8)	8 (8)	6(6)	9(9)	8(8)	8(8)

C. Change in weight and height in the OLE-BSA phase.

	OL-LI baseline to OLE-FD final visit at week 16			
	MTX +adalimumab		adalimumab	
	Same/ decreased dose N=23	Increased dose N=31	Same/ decreased dose N=21	Increased dose N=21
Height(cm)				
Baseline Mean	153	134	152	137
Mean (Median) change	7(4)	17(19)	8(4)	14(17)
Weight(kg)				
Baseline Mean	54	33	52	33
Mean (Median) change	7(6)	12(14)	9(7)	11(11)

[1] baseline mean at OL-LI is based on the available data in each phase
Source Tables: 14.3_5.1.1; 14.3_5.1.2; 14.3_5.2.1; 14.3_5.1

Tanner staging assessment was performed in each phase throughout the study, except FD phase. As noted by the Sponsor and this reviewer, no treatment influence on sequence and rate of

pubertal changes were observed in the study, although no formal statistical comparison was performed.

One significant limitation of the interpretation of data about the effect of adalimumab on growth was the lack of a "no drug exposure" placebo control group since all subjects were exposed to adalimumab in this study. Therefore, no adequate comparison between the active drug group and the placebo control group could be done in the setting of randomized withdrawal design for enriched population. Nonetheless, the data presented above in Table 54 suggest that no potential negative effect on growth was observed with adalimumab treatment.

7.1.16 Overdose Experience

There were no cases of overdosing with adalimumab in the pediatric clinical program.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 171 patients with polyarticular JRA were exposed to adalimumab in study DE038 throughout all four phases of the study. All subjects were administered adalimumab at a dose 24 mg/m^2 of body surface area in the first three phases of the study. One hundred and six subjects were administered doses proposed for licensure, namely 20 mg SQ every other week to children who weighted less than 30 kg and 40 mg SQ every other week to those who weighted 30 kg or greater. Tables 55 and 56 show the extent of exposure to adalimumab in all four phases of the study. The total adalimumab exposure in study DE038 was adequate for pre-approval assessment of both efficacy and safety of adalimumab in the JRA population (also refer to Section 1.2.3).

7.2.1.1 Study type and design/patient enumeration

The updated summary of the duration of exposure in study DE038 is shown in Table 55. Adequate drug exposure was achieved during the study and enabled to perform a pre-approval assessment of safety of adalimumab treatment in children with poly-articular JRA.

Table 55. Number of subjects by duration of treatment.

Duration of treatment	Number of subjects	Percent
1 - 113 DAYS	171	(100)
114 - 197 DAYS	131	(76.6)
198 - 281 DAYS	130	(76.0)
282 - 365 DAYS	128	(74.9)
366 - 449 DAYS	126	(73.7)
450 - 533 DAYS	124	(72.5)
534 - 617 DAYS	116	(67.8)
618 - 701 DAYS	115	(67.3)
702 - 785 DAYS	111	(64.9)
786 - 869 DAYS	108	(63.2)
870 - 953 DAYS	107	(62.6)
954 - 1037 DAYS	105	(61.4)
1038 - 1121 DAYS	103	(60.2)
1122 - 1205 DAYS	92	(53.8)
1206 - 1289 DAYS	73	(42.7)
1290 - 1373 DAYS	44	(25.7)
1374 - 1457 DAYS	24	(14.0)
1458 - 1541 DAYS	14	(8.2)
1542 - 1625 DAYS	5	(2.9)
> 1625 DAYS	1	(0.6)

Data obtained from updated Sponsor's Table 10_1 (Response to IR submitted on Oct 31, 2007)

Also refer to Section 7.2.1.3 for the mean doses and durations of study drug exposure in each phase of the study.

7.2.1.2 Demographics

Refer to Section 6.1.4 for complete demographic information of the studied patient population.

7.2.1.3 Extent of exposure (dose/duration)

The mean exposure in all phases of the study is shown in Table 56.

Table 56. Adalimumab exposure in all four phases of the study.

A. OL-LI and DB phases

	OL-LI			DB					
Exposure to study drug	MTX+ ada N=85	Ada N=86	Overall	MTX+ Placebo N=37	MTX + Adali mumab N=38	Placebo N=28	Adali mumab N=30	Placebo N=65	Adali mumab N=68
Duration, days	97±13	93± 18	95± 16	132 ± 86	155± 97	123± 86	158± 86	128± 85	157± 92
N of injections	8 ± 1	8± 1	8 ± 1	10 ± 6	12 ± 7	9± 6	12± 6	10± 6	12 ± 6
Cumulative dose, mg	241± 66	224 ± 72	232± 70	317± 214	377± 237	302 ± 224	359± 201	310 ± 216	369± 220

B. OLE-BSA phase

	OLE-BSA					
Exposure to study drug	MTX+ Placebo N=36	MTX +adalimumab N=35	Placebo N=28	Adalimumab N=29	Placebo groups N=64	Adalimumab groups N=64
Duration, days	618± 242	658± 203	608 ±221	588± 199	614 ±231	627 ±202
N of injections	43± 17	46± 14	43 ±16	40 ±14	43 ±16	44± 14
Cumulative dose, mg	1382± 672	1515 ±608	1353± 626	1300 ±595	1369± 648	1417± 607

C. OLE-FD phase by treatment assignment

	OLE-FD					
	MTX +Adalimumab		Adalimumab		Overall	
Exposure to study drug	Same/decreased dose N=28	Increased dose N=31	Same/decreased dose N=25	Increased dose N=22	Same/decreased dose N=53	Increased dose N=53
Duration, days	319± 72	336± 4	327± 40	286± 113	323± 59	315 ±76
N of injections	23±6	25± 0.5	23± 3	21± 8	23 ±5	23± 6
Cumulative dose, mg	854± 255	952± 127	837± 247	824 ±333	846 ±249	899± 241

D. OLE-FD phase by dose increase

	Adalimumab increased dose		
Exposure to study drug	5 mg N= 25	10 mg N= 16	>10 mg N=12
Duration, days	318± 67	336 ±4	282± 125
N of injections	24± 5	24± 2	21± 9
Cumulative dose, mg	900 ± 233	949 ±92	830± 369

Data adopted from Table 66 from CSR; Table 3, Table 2.3_1.1 from 120-day safety update and Table 4, Table 2.3_2.1 from 120-day safety update.

There were 55 subjects treated in the OLE-FD phase up to 48 weeks who were also treated with adalimumab in the DB phase. Their total mean exposure was 1278 (157) days, 90 (12) injections and 2992(782) mg of adalimumab. Also refer to Table 55 for additional presentation of cumulative exposure.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.2 Postmarketing experience

Adalimumab was first approved for treatment of RA on December 31, 2002. Through December 2006, adalimumab has been approved in 67 countries with cumulative exposure of [redacted] patient treatment years. The following additional safety information has been obtained based on Abbott Laboratories' ongoing post-approval safety surveillance program for adalimumab, which includes monitoring of clinical studies, spontaneous AE reports, and literature reports:

- Rare cases of serious allergic reactions, including anaphylaxis
- Rare cases of cutaneous vasculitis
- Fatal cases of tuberculosis (TB)
- Rare cases of new onset demyelinating disease, including optic neuritis
- Rare reports of angioneurotic edema
- Rare cases of reactivation of hepatitis B
- Rare cases of interstitial lung disease including pulmonary fibrosis

All of these effects are included in the current version of adalimumab package insert.

7.2.3 Adequacy of Overall Clinical Experience

This application and review rely on the data from pediatric study DE038 for evidence of efficacy and safety of adalimumab in pediatric population with polyarticular JRA. This study provides long term experience with adalimumab in 171 patients with polyarticular JRA. The safety database is adequate for a pre-approval assessment of safety of adalimumab in children with JRA. The safety profile will become more apparent with longer exposure in larger populations of children and may differ from that observed in pre-marketing (Refer to Sections 7.3 and 1.2.3).

7.2.4 Adequacy of Routine Clinical Testing

The applied routine clinical testing in the study DE038 was adequate.

7.2.5 Additional Submissions, Including Safety Update

The original application was submitted on April 26, 2007 and contained data up to week 16 of the OLE-FD phase. A 4-month safety update report was submitted on August 20, 2007 and contained additional safety data for the period between week 16 and week 48 of the OLE-FD

phase. The results reported in the 4-month safety update were combined with the 16 weeks data from the OLE-FD phase and incorporated in different sections of this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

1) Infections

A variety of infections occurring in all systems of organs were observed in study DE038. URIs and viral infections were the most common infectious adverse events occurring in up to 20% of children treated with adalimumab. Notably, herpetic infections, streptococcal pharyngitis and impetigo occurred in all phases of the study regardless of concomitant administration of methotrexate. An increased incidence of infections, primarily URIs and viral, has been observed previously in adult clinical trials with adalimumab and is reported in the product label.

2) Injection site reactions

A higher proportion of adalimumab-treated patients experienced injection site reactions compared to placebo-treated patients. Injection site reactions have been observed previously in clinical trials with adalimumab and are reported in the product label.

3) Cytopenias

Decreases in white blood cell counts, neutrophil counts, platelets, and hemoglobin were observed in children treated with adalimumab. Cases of cytopenias have been observed in adult studies and are included in the current product label.

4) Autoimmunity

Treatment with TNF blockers, including adalimumab, may result in formation of autoantibodies, including ANA, anti-dsDNA and anti-phospholipid antibodies. The observed rate of asymptomatic seroconversion from anti-dsDNA-negative to anti-dsDNA positive status in study DE038 was at least 15/155 (10%) within 48 weeks of treatment. Data on ANA and anti-phospholipid antibodies were not collected in study DE038.

Occurrence of autoimmune phenomena is acknowledged in the current product label. It is recommended to include the observed rates of seroconversion in children treated with adalimumab in the current product label.

5) Immunogenicity

The observed rates of development of anti-adalimumab antibodies were 22/86 (26%) subjects with adalimumab monotherapy and 5/85 (6%) subjects with the combination of adalimumab and

methotrexate. These rates were higher than the rates observed in adult studies (12% with adalmumab alone and 1% with adalimumab and MTX combination). No severe or serious allergic or hypersensitivity reactions were observed in association with anti-adalimumab antibodies.

6) Hypersensitivity

The observed rate of non-serious hypersensitivity reactions was 5-7% in children treated with adalimumab, compared to 1% in the adult RA population.

7) Creatine phosphokinase (CPK) elevation

Elevations in creatine phosphokinase were observed in children treated with adalimumab or the combination of adalimumab and methotrexate. CPK elevations decreased or returned to normal in all cases; the vast majority of the subjects were able to continue treatment with adalimumab. It is recommended that a statement about CPK elevations be added to the ADVERSE REACTIONS section of the label to inform treating physicians about a possibility of development of this laboratory abnormality with adalimumab treatment.

8) Liver function tests (LFTs) elevation

Mild elevations in AST and ALT were observed in several children treated with adalimumab without concomitant MTX. It is recommended to include a statement about occurrence of this laboratory abnormality in the product label.

9) Granuloma annulare

Two children developed granuloma annulare during the course of the study. Granuloma annulare is one of the recently reported events observed in adult patients treated with TNF-blockers, including adalimumab[3]. Granuloma annulare should be included in the ADVERSE REACTIONS section of the label to inform treating physicians about a possibility of development of this uncommon skin lesion that may occur with adalimumab treatment.

10) New onset seizure disorder

One case of new onset seizure disorder was observed during the study DE038 (Section 7.1.3). Cases of new onset or exacerbation of neurologic demyelinating disorders are described in the current product label.

11) Expected serious adverse events known to be associated with adalimumab treatment.

No malignancies, autoimmune disorders, demyelinating disorders, or congestive heart failure (CHF) cases were observed in study DE038. However, the possibility of observing these events in post marketing remains. Therefore, it is the recommendation of this reviewer to request a post

marketing study investigating risk of development of all these serious events, including occurrences of malignancies in the pediatric JRA population. The Sponsor should assemble a registry to collect further information on adverse events that occur at lower frequencies or with longer duration of exposure.

Conclusions:

Overall, the observed safety profile of adalimumab treatment in children with JRA in study DE038 was similar to the safety profile observed in the adult studies with adalimumab for infections, injection site reactions, cytopenias, and LFTs elevations. Compared to adults, higher rates of occurrence of anti-adalimumab antibodies were observed in children treated with adalimumab or concurrently administered adalimumab and methotrexate (6% and 26%). More hypersensitivity reactions were observed in children (5-7%) compared to adults (1%). About 10% of children seroconverted to anti-dsDNA positive status during the study without developing frank autoimmune syndromes. Unlike in clinical studies in adults, elevations in creatine phosphokinase and a few rare cases of granuloma annulare were observed in children with JRA while on adalimumab therapy. No malignancies, opportunistic mycobacterial infections, demyelinating disorders, or CHF were observed in pediatric study DE038. A post-marketing observational study is warranted to further investigate long term safety of adalimumab treatment in the JRA population.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

As indicated previously, in the first three phases of the study the patients were dosed with adalimumab 24mg/m^2 body surface area (BSA) subcutaneously biweekly. Upon entering the OLE-FD phase, the children were receiving 20 mg of adalimumab biweekly if their weight was <30kg and 40 mg of adalimumab biweekly if their weight was ≥30kg. Therefore, upon transition to OLE-FD phase some subjects (n=53) had their dose of adalimumab increased and others (n=53) had their dose of adalimumab decreased or unchanged from what they were receiving in the previous three phases. The original dose/exposure calculation and modeling for the fixed dose regimen are discussed in details in the Clinical Pharmacology review by Dr. Garnett.

Of note, children whose dose of adalimumab was increased in the non-MTX stratum had a median weight of 41 kg (Q 1-Q3: 35kg-48kg) and a median height of 150cm (Q 1-Q3: 143-157cm); they were smaller and younger compared to the children whose dose of adalimumab was decreased or remained the same. About half of the children from the increased dose group weighed between 30 and 40 kg and about 25% of these children weighed between 30 and 35-36 kg (Table 57).

Table 57. Selected demographic characteristics of the study participants at the OLE-FD phase baseline.

Demographic characteristics	MTX stratum		Non-MTX stratum		Overall	
	Same/ Decreased dose N=28	Increased dose N=31	Same/ Decreased dose N=25	Increased dose N=22	Same/ Decreased dose N=53	Increased dose N=53
Age Median (Q1-Q3)	16 (15-18)	12(10-14)	17 (12-17)	12 (9-15)	16(14-18)	12 (10-14)
Age group, years (n, %)						
4-8	2(7)	3(10)	4(16)	3(14)	6(11)	6(11)
9-12	2(7)	14(45)	4(16)	9(41)	6(11)	23(43)
13-21	24(86)	14(5)	17(68)	10(45)	41(78)	24(46)
Body weight, kg, Median (Q1-Q3)	66 (56-77)	46 (36-51)	62(50-76)	41 (35-48)	65(51-76)	45(36-51)
Height, cm, Mean	162	150	159	149	160	149

Table 2.2_2 from 120 day safety update

When the product's dose-concentration relationship was examined for children whose dose of adalimumab was increased, a proportional dose –dependent increase in serum concentration of adalimumab was observed with dose increase, however the exposure range in the OLE-FD phase was similar to that observed in the OLE-BSA phase. (refer to Clinical Pharmacology review by Dr. Garnett).

To evaluate the safety of the fixed dose regimen and to address the question whether an increase in the dose higher then the dose calculated based on the body surface area resulted in any additional safety concerns, the Sponsor compared adverse events rates between the following two groups: 1) children whose dose of adalimumab remained the same or was decreased and 2) children whose dose of adalimumab was increased in the OLE-FD phase.

When proportions of subjects with AEs were compared between the groups at the end of 16 weeks of OLE-FD phase, more infectious AEs were observed in subjects whose dose of adalimumab was increased (non-MTX stratum: 41% in the increased dose group vs 12% in the decreased/same dose group; MTX stratum: 36% in the increased dose group vs 21% in the same/decreased dose group; Table 71, p. 330, CSR). Additionally, more injection site reactions were seen in the increased dose groups compared with decreased/same dose groups in both strata. Analysis of events per 100 person years performed at the end of 16 weeks also demonstrated an increase in the overall number of adverse events primarily comprised of more infectious AEs and injection site reactions related events (data not shown).

Similar analysis was performed at the end of 48 weeks of OLE-FD (Table 58). Overall, the proportions of subjects developing infections were comparable between the groups; more subjects developed injection site reactions among children whose dose of adalimumab was

increased. The observed higher rates of the respective AEs did not appear to be dose-dependent (data not shown).

Table 58. Number and percentage of subjects with AEs at the OLE-FD phase at 48 weeks.

	MTX		Non-MTX		Overall	
Adalimumab dose change	**Same/ Decreased N = 28**	**Increased N = 31**	**Same/ Decreased N = 25**	**Increased N = 22**	**Same/ Decreased N = 53**	**Increased N = 53**
Any AE	23 (82)	24 (77)	17 (68)	19 (86)	40 (75)	43 (81)
Severe AE	3 (11)	2 (6)	3 (12)	2 (9)	6 (11)	4 (8)
Serious AE	2 (7)	0	2 (8)	1 (4)	4 (8)	1 (2)
Infections	14 (50)	17 (55)	11 (44)	10 (46)	25 (47)	27 (51)
Serious infections	0	0	0	1 (4.5)	0	1 (1.9)
Injection site reactions related	2 (7)	4 (13)	0	4 (18)	2 (4)	8 (15)
Hepatic related AE	0	2 (6)	0	0	0	2 (4)
Allergic reaction related	0	0	0	1 (4)	0	1 (2)

Data obtained from Sponsor's Table 7, 120-days safety update.

To examine whether the frequency of AEs increased with increase in exposure to drug (mg/kg of body weight), the Sponsor examined the distribution of AEs among groups with different degrees of exposure to adalimumab (Table 59). The frequency of injection site reactions tended to increase with increased exposure, whereas the rate of infections did not appear to increase.

Table 59. Distribution of AEs according to drug exposure in mg/kg of body weight at 48 weeks OLE-FD phase.

	Min - <P5 N = 5	P5 -< P25 N = 23	P25-<P50 N = 25	<P50-< P75 N = 26	P75 -< P95 N = 21	P95 – Max N = 6
Any AE	4 (80)	18 (78)	17 (68)	21 (81)	18 (86)	5 (83)
Severe AE	0	5 (22)	1 (4)	2 (8)	2 (10)	0
Serious AE	1 (20)	3 (13)	0	0	1 (5)	0
Infections	2 (40)	13 (56)	11 (44)	12 (46)	11 (52)	3 (50)
Serious infections	0	0	0	0	1 (5)	0
Injection site reactions	0	0	1 (4)	3 (12)	6 (29)	0
Hepatic related AE	0	0	0	0	1 (5)	1 (17)
Allergic reaction related	0	0	0	0	1 (5)	0

P = percentile Min -< P5 = 0.37-<0.46, P5 - <P25 = 0.46 -<0.62, P25-<P50 = 0.62-< 0.78, P50 - < P75 = 0.78- <0.93, P75 -< P95 = 0.93 -<1.23, P95 – Max = 1.23 -< 1.31

Data from Sponsor's Table 9, 120-day safety update.

Of note, the children who were in the upper quartile of drug exposure (>=75 percentile) and receiving the highest exposure to adalimumab would be those children whose weight would be approximately between 30 and 40 kg. An exploratory comparison of the proportions of adverse events occurring in children from different weight categories (16 week data from OLE-FD phase) was performed and is shown in the Clinical Pharmacology review by Dr. Garnett. The rate of infectious complications was not increased among children whose weight was between 30 and 40 kg and who received the highest adalimumab exposure.

To examine whether the frequency of AEs increased over time, the Sponsor compared rates of events at the different time periods (Table 60). The AEs occurrence did not increase over time; in fact, the occurrence of injection site reactions and serious AEs appeared to decrease with long term treatment.

Table 60. Distribution of AEs over time, OLE-FD phase.

Adverse Event n (%)	Days 1 – 112 N= 106	Days 113 – 224 N = 102	Days 225 – 336 N = 100	Days ≥ 337 N = 83
Any AE	61 (58)	50 (49)	53 (53)	25 (30)
Serious AE	4 (4)	1 (1)	1 (1)	1 (1)
Severe AE	5 (5)	2 (2)	5 (5)	2 (2)
Infections	31 (29)	22 (22)	30 (30)	7 (8)
Serious infections	1 (1)	0	0	0
Injection site reactions	6 (6)	7 (7)	3 (3)	2 (2)
Hepatic related	1 (1)	0	1 (1)	0
Allergic reactions	1 (1)	0	0	0

Data obtained from Sponsor's Table 10; 120-day safety update.

Overall, the data suggest that there was an apparent trend toward an increase in adverse events related to injection site reactions in patients whose dose was increased in the OLE-FD phase. As pointed out by the Sponsor, the larger volume of the product received upon dose increase could explain the higher rates of injection site reactions.

The initially apparent trend of increase in infections was not seen in the subsequent analyses including analysis by exposure and by weight. Apart from the change in the product exposure, it is possible that the inconsistent signal in the infectious AEs could be explained by the differences in demographic characteristics of the compared groups of children; i.e. younger children get transient infections more frequently than older children.

To further understand whether the children whose dose was increased had more adverse events in the OLE-FD phase compared with the time when they were still receiving individually tailored dosing based on body surface area, the AE rates during the OLE-BSA phase and the OLE-FD phase were compared for the population of children participating in the OLE-FD phase. For the OLE-BSA phase, the groups of children were retrospectively broken into dose assignments that they would later receive in the OLE-FD phase. To overcome the inequality in durations of the phases, analysis of events per 100 person years was performed (data not shown). That analysis demonstrated that the number of events per 100 person years in all categories has numerically decreased in all treatment groups from OLE-BSA phase to OLE-FD phase.

In conclusion, children who had their dose increased upon switch to the fixed dose regimen had more injection site reactions (mainly observed in those weighing between 30 and 40 kg) upon dose increase compared to those children who had their dose left the same or decreased (primarily older children weighing >40 kg). When the rates of adverse events were compared in children who had their dose increased before and after the dose change, no increase in occurrence of adverse events was observed. The children with the higher levels of exposure did not have more infections compared to children receiving the lower exposure levels. No increase in injection site reactions was seen with longer duration of treatment.

Although reassuring, these conclusions have certain limitations. In this study, any signals in the occurrence of adverse events upon dose change are confounded by the previous exposure to adalimumab (duration of treatment, individual tolerance for locally injected volume and systemic effects). The non-randomized comparison between the groups of "drug survivors" different in their demographic characteristics makes the interpretation of the data even more difficult and prone to error.

Overall, the data suggest that the dosing regimen for pediatric patients proposed by the Sponsor appears adequate. Also refer to Clinical Pharmacology review by Dr. Garnett.

8.2 Drug-Drug Interactions

Specific drug-drug interactions were not formally studied in this pediatric clinical development program. In adults, the biologic TNF blockers class of drugs is not recommended to be used

concomitantly with other biologics such as anakinra, abatacept and rituximab. Given that there are no data to complete a risk benefit assessment of adalimumab in combination with other biologic DMARDs in children with poly-articular JRA, adalimumab should not be used in combination with other biologic therapies until there are adequate supporting data.

8.8 Other Relevant Materials

[redacted]

9 OVERALL ASSESSMENT

9.1 Conclusions

1. Adalimumab is effective for the treatment of patients with moderate to severe poly-articular JRA. This assessment is based on a significant effect size substantiated in one adequate and well-controlled pediatric study DE038. Treatment with adalimumab was associated with fewer flares in a randomized withdrawal study and with improvement of signs and symptoms in children with poly-articular JRA. The study was adequately large, multi-center, and placebo-controlled, providing statistically persuasive evidence of benefit. The consistency of adalimumab's effects across different endpoints provides convincing evidence of efficacy.

2. In view of the demonstrated efficacy, adalimumab has an acceptable safety profile for the treatment of children with moderate to severe poly-articular JRA [redacted] This assessment is based on data from 171 children enrolled in study DE038 that included both long-term treatment and treatment with the proposed fixed dose regimen.

3. Efficacy and safety of adalimumab in children with JRA who failed treatment with one or more biologics was not studied in study DE038. Therefore, a clarification should be added to the pediatric study description in the product label, indicating that the effects of Humira ® in pediatric patients not responding to one or more *biologic* DMARDs were not studied.

4. The adverse event profile in children was similar to adults in regards to increased incidence of infections, injection site reactions, cytopenias, and liver function tests elevations. The rate of infections in patients treated with adalimumab monotherapy was

20% in the DB phase of the study. These events were primarily upper respiratory and viral infections.

5. Adalimumab was more immunogenic in children and caused more non-serious hypersensitivity reactions compared to adults. Unlike in adults, elevations in the muscle enzyme, creatine phosphokinase, were observed in children treated with adalimumab. The rates of injection site reactions, immunogenicity, hypersensitivity reactions, and autoantibody formation observed in pediatric population should be added to the product label. The following adverse events occurring in pediatric population should be added to the ADVERSE EVENTS section: CPK elevation, liver function test elevation, granuloma

6. Although malignancies, opportunistic infections including mycobacterial infections, demyelinating disorders, autoimmune disorders, or cases of congestive heart failure were not observed in the pediatric study DE038, a possibility of observing these events in post-marketing remains owing to the known effects of the TNF blockers.

7. As recommended in the current product label, Humira® should not be given with live vaccines. This specific of product administration may affect pediatric population where vaccinations with live attenuated vaccines are among the obligatory vaccinations and revaccinations for young children recommended by the Center for Disease Control and Prevention. To minimize possible delays or avoiding of the recommended vaccinations in young children with poly-articular JRA treated with Humira®, a statement that pediatric patients of appropriate age, whenever feasible, should be offered vaccinations or re-vaccination with live attenuated vaccines prior to treatment with adalimumab should be added to the product label.

9.2 Recommendation on Regulatory Action

Adalimumab should be approved for reducing signs and symptoms in children with moderately to severely active poly-articular course JRA with appropriate revisions to the proposed label.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Humira® currently has a MedGuide that informs patients and parents about the potential risks of the product. Additionally, the product label provides complete information on occurrences of adverse events associated with Humira®. Adverse events observed in the post marketing experience will be submitted to the Agency as part of standard pharmacovigilance.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

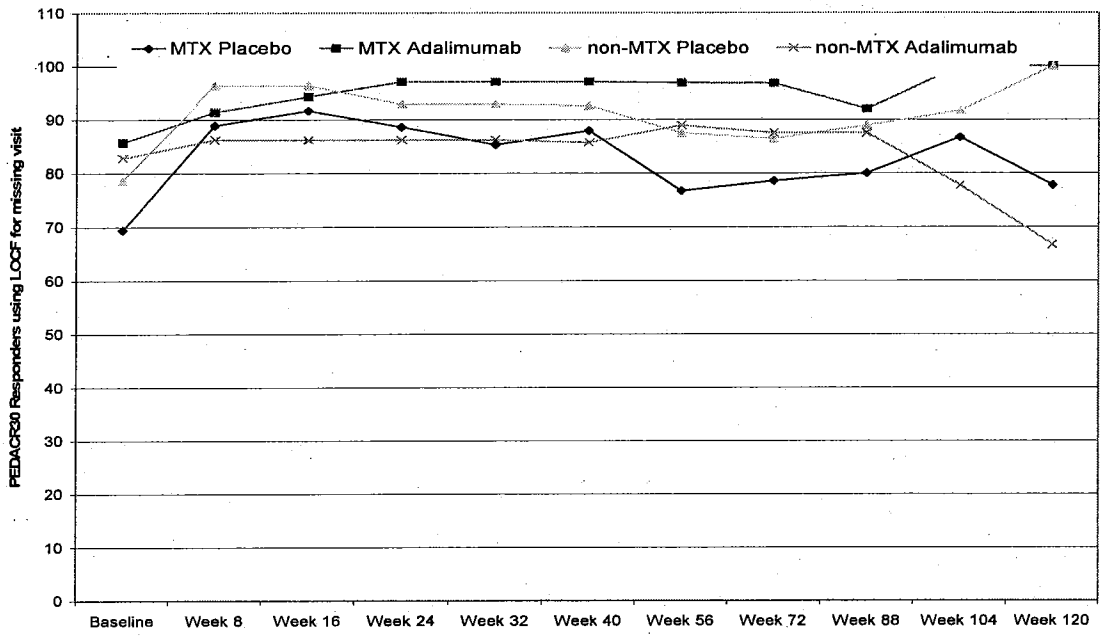
As indicated in Section 2.5 of this review, previous agreement about assembling a registry of the children treated with adalimumab was reached by the Division and the Sponsor during the pre-sBLA meeting on Feb 1, 2007.

[redacted]

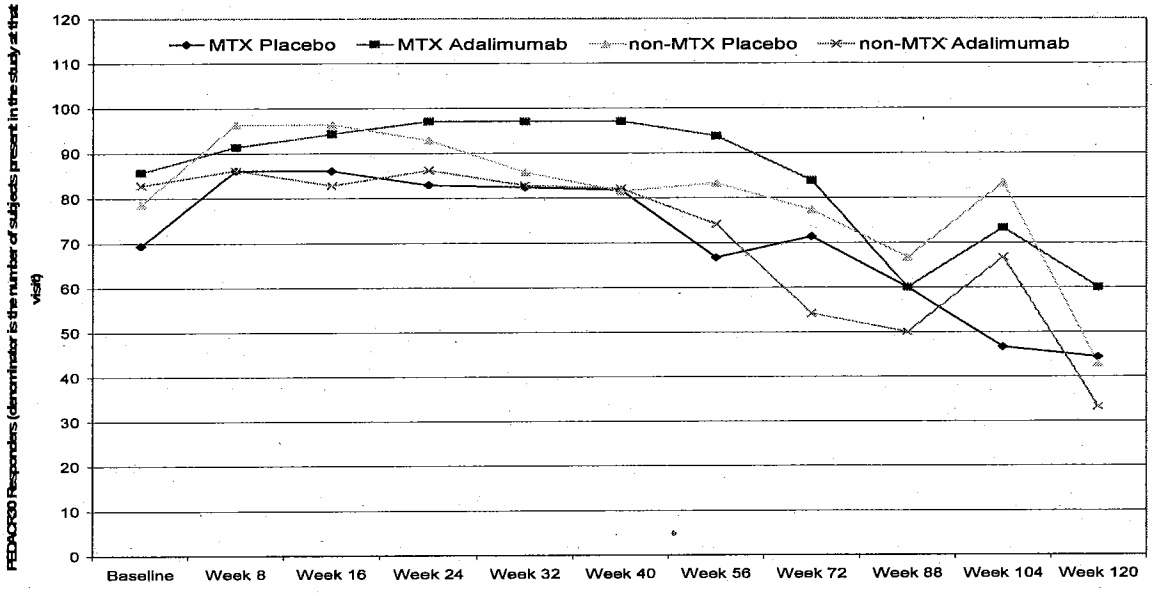
10 APPENDICES

APPENDIX A. Pediatric ACR responses in the OLE-BSA phase (refer to Section 6.1.6).

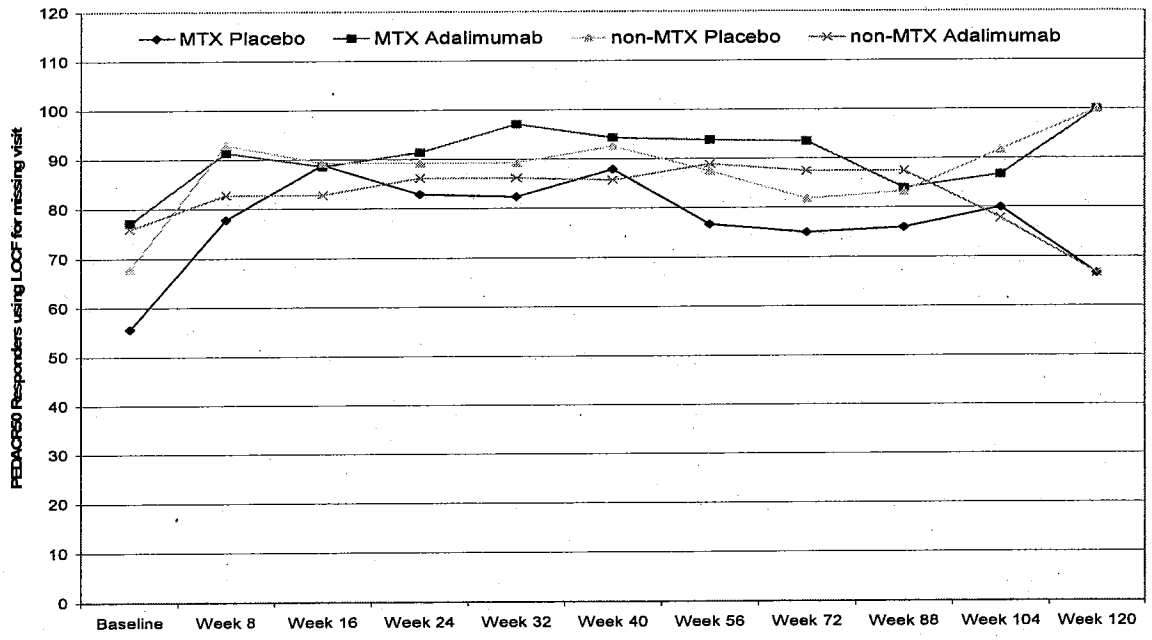
1. PedACR 30 from analysis #2.



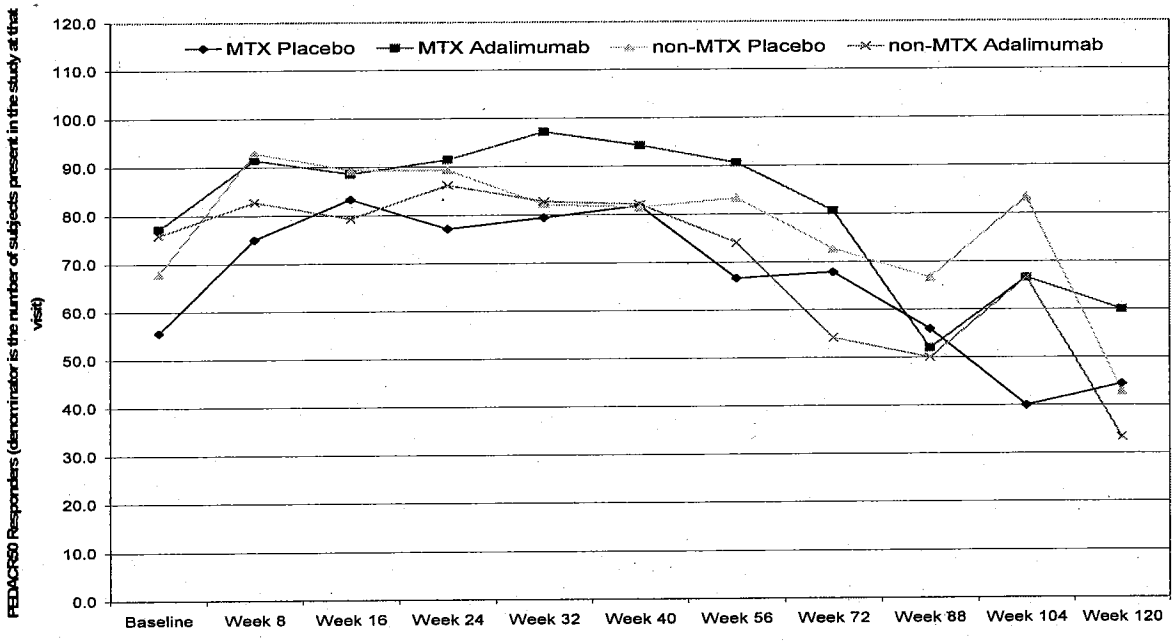
PedACR 30 from analysis #4.



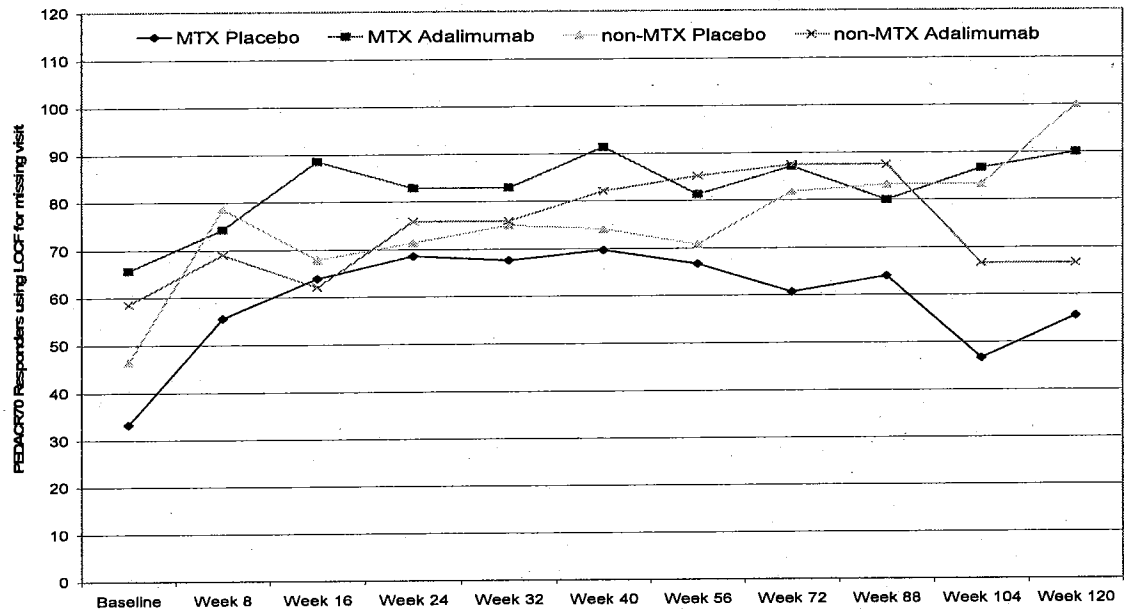
2. PedACR 50 from analysis #2



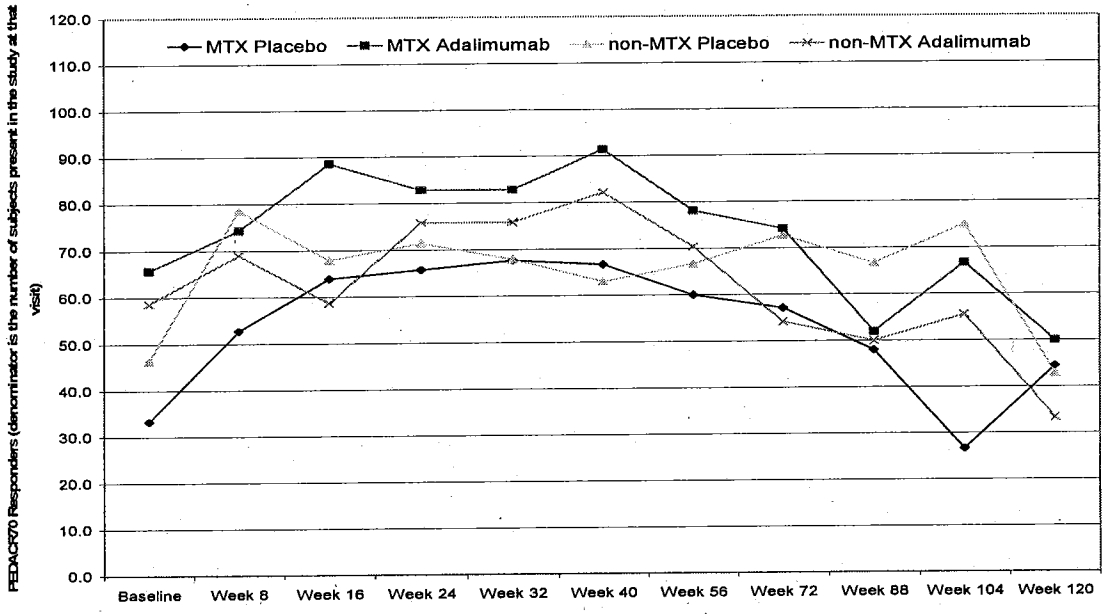
PedACR 50 from analysis #4



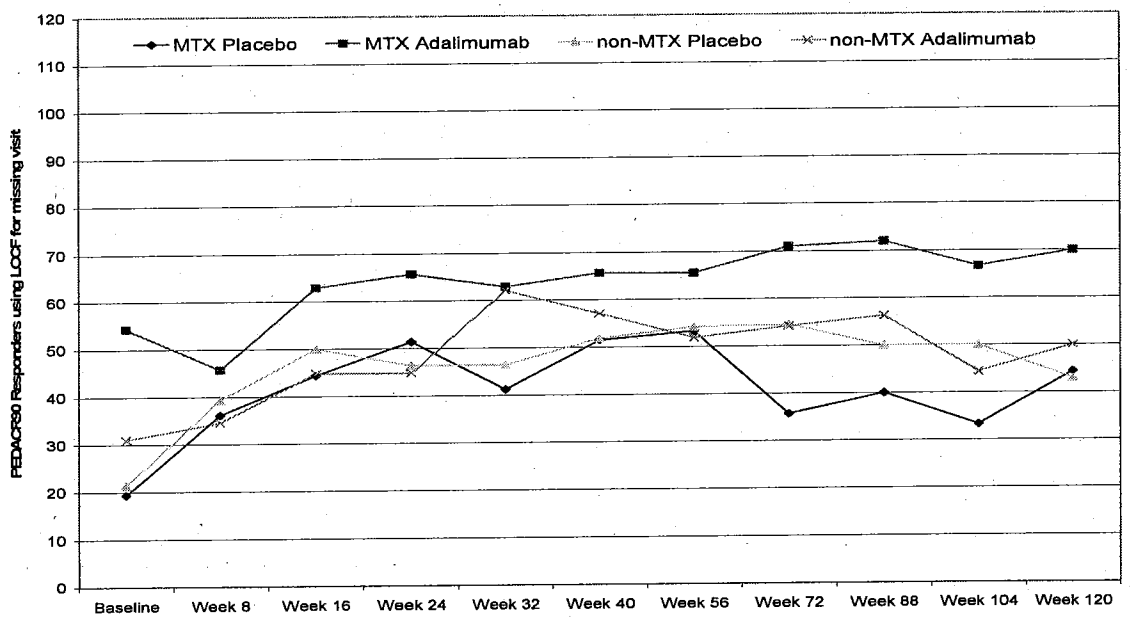
3. PedACR 70 from analysis #2.



PedACR 70 from analysis #4



4. PedACR 90 from analysis #2



PedACR 90 from analysis #4

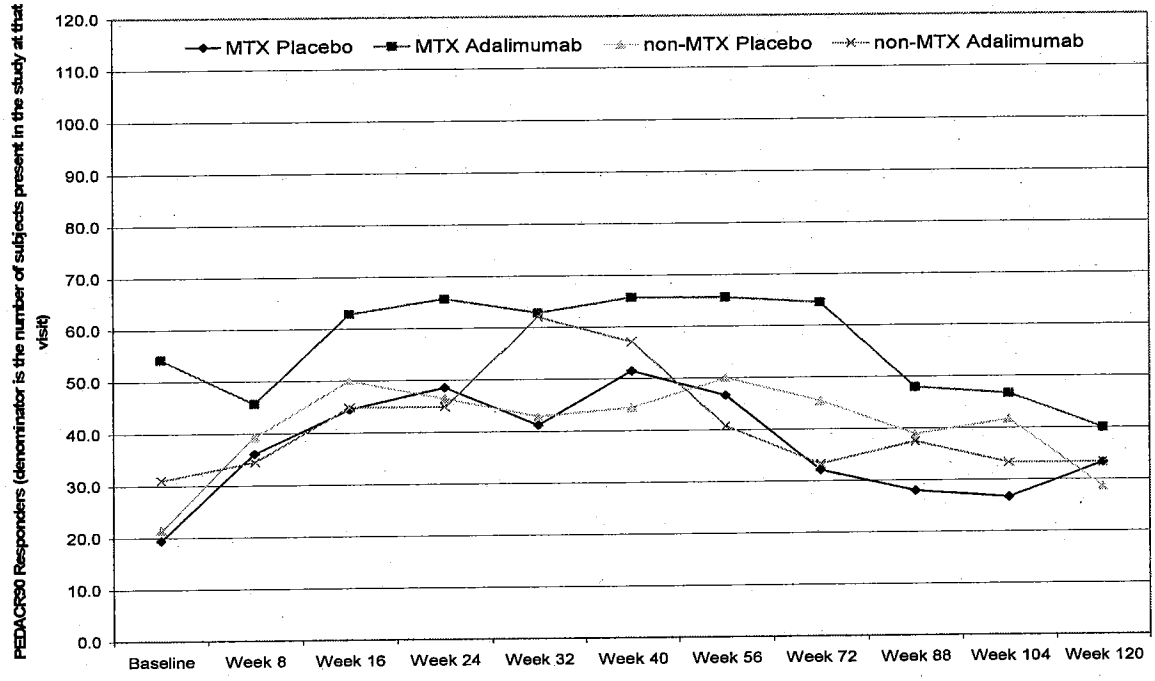


Table A. Maintenance of PedACR response rates on the OLE-BSA phase in both strata based on the proportion of PedACR responders according to analysis #4.

	Adalimumab + MTX during the OLE-BSA phase		Adalimumab monotherapy during the OLE-BSA phase	
Time points (clinical visits)**	MTX alone during the DB phase	MTX + adalimumab during the DB phase	Placebo during the DB phase	Adalimumab during the DB phase
PedACR 30 responders				
Baseline*	25/36 (69%)	30/35(86%)	22/28 (79%)	24/29 (83%)
Week 8	31/36 (86%)	32/35(91%)	27/28(96%)	25/29(86%)
Week 32	28/34 (82%)	34/35(97%)	24/28(86%)	24/29(83%)
Week 40	27/33(82%)	34/35(97%)	22/27(81%)	23/28(82%)
Week 56	20/30 (67%)	30/32(94%)	20/24(83%)	20/27(74%)
Week 72	20/28 (71%)	26/31(84%)	17/22(77%)	13/24(54%)
Week 88	15/25 (60%)	15/25(60%)	12/18(67%)	8/16(50%)
PedACR 50 responders				
Baseline*	20/36 (56%)	27/35(77%)	19/28 (68%)	22/29(76%)
Week 8	27/36(75%)	32/35(91%)	26/28(93%)	24/29(83%)
Week 32	27/34(79%)	34/35(97%)	23/28(82%)	24/29(83%)
Week 40	27/33(82%)	33/35(94%)	22/27(81%)	23/28(82%)
Week 56	20/30(67%)	29/32(91%)	20/24(83%)	20/27(74%)
Week 72	19/28(68%)	25/31(81%)	16/22(73%)	13/24(54%)
Week 88	14/25(56%)	13/25(52%)	12/18(67%)	8/16(50%)
PedACR 70 responders				
Baseline*	12/36 (33%)	23/35(66%)	13/28(46%)	17/29(59%)
Week 8	19/36(53%)	26/35(74%)	22/28(79%)	20/29(69%)
Week 32	23/34(68%)	29/35(83%)	19/28(68%)	22/29(76%)
Week 40	22/33(67%)	32/35(91%)	17/27(63%)	23/28(82%)
Week 56	18/30(55%)	25/32(78%)	16/24(67%)	19/27(70%)
Week 72	16/28(57%)	23/31(74%)	16/22(73%)	13/24(54%)
Week 88	12/25(48%)	13/25(52%)	12/18 (67%)	8/16(50%)
PedACR 90 responders				
Baseline*	7/36 (19%)	19/35(54%)	6/28 (21%)	9/29(31%)
Week 8	13/36 (36%)	16/35(46%)	11/28(39%)	10/29(34%)
Week 32	14/34(41%)	22/35(63%)	12/28(43%)	18/29(62%)
Week 40	17/33(52%)	23/35(66%)	12/27(44%)	16/28(57%)
Week 56	14/ 30(47%)	21/32(66%)	12/24(50%)	11/27(41%)
Week 72	9/28(32%)	20/31(65%)	10/22(45%)	8/24(33%)
Week 88	7/25(28%)	12/25(48%)	7/18(39%)	6/16(38%)

Data obtained from Sponsor's Tables 53-56, p 288, CSR and Tables 3-6, p19, Response to IR.
* the baseline values represent the observed PedACR responses at the time of entering the OLE-BSA phase regardless of flare occurrence in the DB phase;

APPENDIX B. Listings of infectious AEs occurring in single patients in Study DE038.

OL-LI phase: Among subjects treated with combination of adalimumab and MTX, infections reported in single subjects included:

- acute sinusitis,
- bacterial infection,
- cellulitis,
- enterobiasis,
- fungal skin infection,
- laryngitis,
- acute otitis media,
- tinea versicolour,
- tonsillitis,
- tracheobronchitis.

Among subjects treated with adalimumab alone, infections reported in single subjects included:

- beta-hemolytic streptococcal infection,
- infectious diarrhea,
- viral gastritis,
- herpes virus infection,
- kidney infection,
- nail infection,
- oral candidiasis,
- pyoderma streptococcal.

DB phase: In the non-MTX stratum, infectious AEs occurring as single cases in association with adalimumab treatment that were not observed in placebo group included:

- bronchitis,
- febrile infection,
- fungal skin infection,
- Herpes simplex,
- Herpes virus infection,
- impetigo.

In the MTX stratum, infectious AEs occurring as single cases in subjects treated with combination of MTX and adalimumab that were not observed in the subjects treated with placebo or with MTX alone included:

- acute viral bronchitis,
- furuncle,
- kidney infection,
- varicella
- vulvovaginitis.

The following AEs were observed among subjects treated with MTX with and without adalimumab but not observed in placebo treated group: scarlet fever (2), otitis media (2) and otitis externa (1)- data from Sponsor's source Table 14.3_1.3.1.2.

OLE-BSA: Single infectious AEs reported with adalimumab alone (data from Sponsor's Table 14.3_1.4.1) included:

- bronchopneumonia,
- infective conjunctivitis,
- cystitis,
- infectious enteritis,
- eye infection,
- fungal infection,
- gastroenteritis caused by Salmonella,
- genital candidiasis,
- herpetic gingivostomatitis,
- hordeolum,
- lice infestation,
- molluscum contagiosum,
- onychomycosis,
- pustular rash,
- bacterial skin infection,
- staphylococcal infection,
- tinea infection,
- tinea versicolour,
- tracheitis.

Single infectious AEs reported with combination of MTX and adalimumab (data from Sponsor's Table 14.3_1.4.1) included:

- bacterial infection,
- bronchopneumonia,
- fungal infection,
- viral gastroenteritis,
- gastrointestinal infection,
- Hemophilus infection,
- Herpes virus infection,
- infected cyst,
- laryngopharyngitis,
- scarlet fever,
- skin bacterial infection,
- streptococcal infection,
- Tinea infection,
- Tinea versicolour,
- tracheitis,
- viral rash,
- wound infection.

OLE-FD phase: Single infectious AEs associated with increase in the adalimumab dose in the MTX stratum included:

- bacteriuria,
- otitits media (1 case in each stratum),
- acute otitis media,

- tonsillitis (1 in each stratum),
- tracheitis,
- tracheobronchitis,
- urinary tract infection.

In the non-MTX stratum, single AEs associated with increase in adalimumab dose included:

- chest wall abscess,
- impetigo.

Two cases of infectious mononucleosis and gastroenteritis occurred in the OLE-FD phase equally in the same/decreased dose and the increased dose groups.

APPENDIX C Common adverse events observed with long term adalimumab treatment.

Table Adverse events observed in >=5% of subjects in OLE-BSA phase, AEs ranked for the adalimumab monotherapy group.

Preferred Term	MTX +Adalimumab N=71	Adalimumab N=57	Adalimumab (previously placebo) N=64	Adalimumab continued through DB and OLE-BSA, N=64
Upper respiratory infection	20(28)	19 (33)	20 (31)	19 (30)
Viral infection	14 (20)	10(18)	11 (17)	13 (20)
Injection site reaction	8 (11)	9 (16)	9 (14)	8 (12)
Headache	9 (13)	8 (14)	13 (20)	4 (6)
Sinusitis	7 (10)	7(12)	5 (8)	9 (14)
Rheumatoid arthritis	7 (10)	7(12)	8 (12)	6(9)
Injection site pain	10 (14)	6 (10)	8(12)	8(12)
Arthralgia	5 (7)	6(10)	3(5)	8(12)
Pyrexia	4 (6)	6(10)	4(6)	6(9)
Pharyngitis streptococcal	3(4)	6(10)	3(5)	6(9)
Injection site irritation	5(7)	5 (9)	6(9)	4(6)
Cough	4(6)	5 (9)	3 (5)	8 (12)
Impetigo	2(3)	5 (9)	3(5)	4(6)
Otitis media	2(3)	5 (9)	5(8)	2(3)
Rash	5(7)	4(7)	7(11)	2(3)
Pharyngitis	10 (14)	4(7)	8(12)	6(9)
Nasopharyngitis	9(13)	4(7)	5(8)	8(12)
Juvenile arthritis	7 (10)	4(7)	6(9)	5(8)
Excoriation	7 (10)	4(7)	6(9)	5(8)
Urinary tract infection	5(7)	4(7)	4(6)	5(8)
Viral upper respiratory tract infection	3(4)	4(7)	4(6)	3 (5)
Joint sprain	1(1)	4(7)	0	5(8)
Muscle strain	1(1)	4(7)	2(3)	3 (5)
Conjunctivitis	0	4(7)	2(3)	2(3)
Vomiting	5(7)	3(5)	7(11)	1(<2)
Nausea	9(13)	3(5)	7(11)	5(8)
Contusion	4(6)	3(5)	4(6)	3 (5)
Dysmenorrhoea	2(3)	3(5)	2(3)	3 (5)
Skin papilloma	2(3)	3(5)	2(3)	3 (5)
Muscle spasms	1(1)	3(5)	0	4(6)
Influenza	1(1)	3(5)	2(3)	2(3)
Tonsillar hypertrophy	1(1)	3(5)	4(6)	0
Pain	0	3(5)	2	1(<2)

Data obtained from Sponsor's Table 80 and Table 14.3_1.6.1, CSR

APPENDIX D. Less common adverse events observed study DE038.

OL-LI phase

Less common AEs occurring in <5% - >= 2 subjects treated with adalimumab alone included: ear pain(2), eye pain(2), abdominal discomfort(2), diarrhea(3), vomiting (2), pyrexia(2), ear infection (2), blood creatine phosphokinase increased (2), dizziness (3), allergic rhinitis(2), dermatitis(2), dry skin (3), erythema(3), pruritis (3), papular rash(2), skin lesion (2).

Less common AEs occurring in <5% - >= 2 subjects treated with combination of adalimumab and MTX included: abdominal pain(3), upper abdominal pain (2), diarrhea(2), gastritis(2), mouth ulceration (2), vomiting (4), fatigue (2), liver disorder (2), joint sprain (3), skin laceration (4), alanine aminotransferase increased (3), aspartate aminotransferase increased (2), arthralgia (4), back pain (2), juvenile arthritis (2), myalgia (4), menorrhagia (2), epistaxis (2), rhinorhea (4).

DB phase

The following AEs were reported as single cases in association with adalimumab monotherapy and did not occur among the placebo-treated subjects: neutropenia, Eustachian tube dysfunction, myopia, aphthous stomatitis, calcinosis (unrelated to study treatment), back injury, concussion, laceration, bursitits, myofascial pain syndrome, tension headache, hematuria, neurogenic bladder, allergic rhinitis, tonsillar hypertrophy, hemorrhage (unrelated to study treatment).

The following AEs occurred as single cases in subjects treated with combination of MTX and adalimumab: leucopenia, conjunctivitits, lower abdominal pain, cheilosis, foot fracture, hand fracture, joint injury, sunburn, alanine aminotransferase increased, aspartate aminotransferase increased, lymphocyte count increased, neutrophil count decreased, neck pain, dizziness, orthostatic proteinuria, and epistaxis.

One subject treated with the combination of adalimumab and MTX in the OL-LI phase later randomized into MTX only treatment group developed a cytomegalovirus infection.

OLE-BSA phase

Table shows rates of less common AEs occurring in <5% subjects with long term treatment in the OLE-BSA phase.

Table D1. AEs occurring in <5% subjects while on adalimumab treatment. The AEs are ranked in the adalimumab monotherapy group (non-MTX stratum).

	OLE-BSA			
	MTX +Adalimumab N=71	Adalimumab N=57	Adalimumab (previously placebo) N=64	Adalimumab continued through DB and OLE-BSA, N=64
Arthropod bite	4(6)	2(4)	3(5)	3(5)
Rhinitis	4(6)	2(4)	4(6)	2(3)
Abdominal pain	3(4)	2(4)	2(3)	3 (5)
Acne	3(4)	2(4)	2(3)	3 (5)
Diarrhoea	3(4)	2(4)	3(5)	2(3)
Lymphadenopathy	2(3)	2(4)	1(<2)	3 (5)
Gastroenteritis	2(3)	2(4)	1(<2)	3 (5)
Syncope	2(3)	2(4)	1(<2)	3 (5)
Hypersensitivity	2(3)	2(4)	3(5)	1(<2)
Dizziness	2(3)	2(4)	4(6)	0
Fatigue	2(3)	2(4)	4(6)	0
Adenoidal hypertrophy	1(1)	2(4)	3(5)	0
Gastroenteritis viral	1(1)	2(4)	3(5)	0
Gastrointestinal infection	1(1)	2(4)	3(5)	0
Myopia	0	2(4)	2(3)	0
Nasal congestion	0	2(4)	2(3)	0
Rhinitis allergic	0	2(4)	2(3)	0
Bronchitis	4(6)	1(2)	3(5)	2(3)
Influenza like illness	4(6)	1(2)	4(6)	1(<2)
Arthritis	5(7)	1(2)	1(<2)	5(8)
Transaminases increased	3(4)	1(2)	1(<2)	3 (5)
Eye infection	3(4)	1(2)	2(3)	2(3)
Paronychia	3(4)	1(2)	2(3)	2(3)
Injury	3(4)	1(2)	3(5)	1(<2)
Laceration	2(3)	1(2)	0	3 (5)
Neck pain	2(3)	1(2)	1(<2)	2(3)
Dermatitis contact	5(7)	0	3(5)	2(3)
Acute tonsillitis	4(6)	0	1(<2)	3(5)
Pharyngolaryngeal pain	6(8)	0	2(3)	4(6)
Pain in extremity	4(6)	0	2(3)	2(3)
Ear infection	4(6)	0	3(5)	1(<2)
Anxiety	2(3)	0	0	2(3)
Back pain	2(3)	0	0	2(3)
Infectious mononucleosis	2(3)	0	0	2(3)
Skin laceration	2(3)	0	0	2(3)
Tinea pedis	2(3)	0	0	2(3)

Data obtained from Sponsor's Table 80 and Table 14.3_1.6.1, CSR

Other AEs occurring in <5% subjects treated with adalimumab alone: ear pain, constipation, gastritis, food poisoning, stomatitis, asthenia, foot fracture, increased blood creatinine phosphokinase, asthma. (Sponsor's Table 14.3_1.4.1).

OLE-FD phase

Table D2. AEs observed in <2 subjects in OLE-FD phase, AEs ranked for the adalimumab increased dose group.

	MTX+adalimumab		Adalimumab alone		Overall	
Adalimumab dose change	**Same/ Decreased N = 28**	**Increased N = 31**	**Same/ Decreased N = 25**	**Increased N = 22**	**Same/ Decreased N = 53**	**Increased N = 53**
Proportion of subjects with any Adverse Events (one or more), n(%)	23(82)	24(77)	17(68)	19(86)	40(75)	43(81)
Adverse Events by MedDRA Preferred Term, n(%)						
Pharyngitis	2 (7)	1 (3)	0	0	2 (4)	1 (2)
Rheumatoid arthritis	2(7)	0	0	1(4)	2(4)	1(2)
Cough	1(4)	0	0	1(4)	1(2)	1(2)
Abdominal pain	2(7)	1(3)	0	0	2(4)	1(2)
Rash	2(7)	0	1(4)	1(4)	3(6)	1(2)
CPK increased	0	1(3)	1(4)	0	1(2)	1(2)
Gastroenteritis viral	3(11)	0	0	0	3(6)	0
Constipation	1(4)	0	1(4)	0	2(4)	0
Vomiting	1(4)	0	1(4)	0	2(4)	0
Dysmenorrhea (including metrorrhagia)	3 (10)	0	0	0	3 (6)	0

Data source: Sponsor's Tables 81; 82; 14.3_1.4.2.1 from the original submission, Table 13, Table 2.4_1.3.1 from 120-day safety update

Isolated cases reported in association with increased adalimumab dose in the MTX stratum included: conjunctivitis, gastritis, chest pain, cyst, face injury, joint injury, skeletal injury, ALT increased, AST increased, weight decreased, LFTs abnormal, disturbance in attention, aggression, depressed mood, allergic rhinitis, urticaria. Isolated cases occurring in association with increased adalimumab dose in the non-MTX stratum included: upper abdominal pain, dyspepsia, nausea, toothache (2), peripheral edema, chest wall abscess, incision site complication, acute mountain sickness, scratch, hypercholesterolemia, myalgia, bone pain, musculoskeletal pain, nervousness, asthma, nasal congestion, allergic dermatitis.

APPENDIX E. Changes in chemistry parameters in study DE038.

Table E1. Mean changes in chemistry parameters in the OL-LI and DB phases.

	OL-LI		DB				OL-LI and DB			
	Mean changes from OL-LI baseline at Week 16		Mean changes from DB baseline at week 48				Mean changes from OL-LI baseline at week 48			
	MTX+ ada N=81	Ada N=76	MTX+ Placebo N=15	MTX +ada N=22	Placebo N=9	Ada N=17	MTX+ Placebo N=15	MTX +ada N=22	Placebo N=9	Ada N=17
Albumin (g/dl)										
Baseline	4.2	4.1	4.5	4.4	4.4	4.3	4.3	4.2	4.1	4.1
Change	0.2	0.2	-0.2	0.01	0.04	0.05	0.07	0.2	0.4	0.3
ALT (IU/L)										
Baseline	18	15	18	18	16	17	17	20	15	14
Change	1.3	1.2	-0.7	2	2.8	3.5	-0.1	-0.8	3.7	6
AST (IU/L)										
Baseline	23	23	25	24	23	25	24	24	20	24
Change	1.3	1.3	-0.3	0.8	0.3	1.1	0.3	0.9	3	2
Bicarbonate (mEq/L)										
Baseline	21	22	21	21	21	21	22	22	22	21
Change	-0.08	-0.13	1.4	0.5	0.9	-0.4	0.5	-0.08	0.4	-0.4
BUN(mg/dl)										
Baseline	14	15	12	13	16	15	12	13	17	15
Change	0.2	-0.3	-0.4	-0.8	-1.2	0.2	-0.1	-0.6	-2	0.2
Calcium (mmol/L)										
Baseline	9.9	9.9	9.9	9.8	10	9.8	9.9	9.9	9.9	9.9
Change	-0.07	-0.04	-0.2	0.07	0.06	0.2	-0.3	-0.04	0.2	0.08
Chloride (mEq/L)										
Baseline	106	106	106	106	106	106	106	106	106	106
Change	0.2	-0.2	-0.6	-2.6	-1.3	-0.5	-0.7	-1.4	-2	-0.5
CPK (IU/L)										
Baseline	67	74	100	92	94	102	80	66	74	76
Change	26	22	-10	5	30	-0.2	10	31	49	26
Creatinine (µmol/L)										
Baseline	0.5	0.5	0.5	0.5	0.6	0.5	0.5	0.5	0.6	0.5
Change	0.02	0.03	0.06	0	0.07	0.06	0.09	0.02	0.09	0.08
GGT(U/L)										
Baseline	12	14	12	11	12	11	13	12	12	12
Change	-0.8	-0.9	1.2	0.13	-0.8	-1.3	0.3	-0.2	-1.2	-2.4
Glucose(mmol/L)										
Baseline	88	89	85	103	85	93	85	89	86	90
Change	3.5	2.6	5	-13	3	-7	4.9	1.5	1.9	-4.6
Inorganic phosphorus (mg/dl)										
Baseline	4.4	4.6	4.5	4.6	4.5	4.7	4.4	4.5	4.4	4.8
Change	0.2	-0.03	-0.15	-0.01	0.06	0.15	-0.1	0.2	0.1	0.1
LDH(IU/L)										
Baseline	189	181	193	179	166	190	194	184	159	185

Change	-2.5	1.7	-4	4	2	3	-5	-1	9	8
Potassium (mEq/L)										
Baseline	4.3	4.3	4.1	4.3	4.4	4.2	4.3	4.2	4.6	4.3
Change	-0.03	-0.12	0.13	-0.03	-0.03	0.07	-0.01	0	-0.2	-0.08
Sodium (mEq/L)										
Baseline	141	141	141	142	140	140	141	141	140	140
Change	-0.02	-0.3	0.5	-2.6	0.9	1.5	-0.3	-1.5	0.9	1.4
Bilirubin total (mg/dl)										
Baseline	0.4	0.3	0.5	0.4	0.4	0.3	0.4	0.4	0.3	0.3
Change	0.04	0.03	-0.15	0.06	0.01	-0.01	0.25	0.03	0.03	0.02
Total Cholesterol (mg/dl)										
Baseline	152	155	158	155	150	156	153	147	146	150
Change	7	4	-1.8	0.4	3	6	3	9	7	12
Total protein (g/dl)										
Baseline	7.6	7.6	7.3	7.5	7.8	7.5	7.3	7.5	7.9	7.6
Change	-0.1	-0.07	0.3	0.04	-0.06	0.09	0.3	-0.02	-0.2	-0.01
TG (mmol/L)										
Baseline	93	101	103	108	117	103	96	88	78	77
Change	21	18	3	-11	6	-20	10	9	45	6
Uric acid (mmol/L)										
Baseline	4	4	4	4	4	4	4	4	4	4
Change	-0.06	-0.06	0.12	0.07	-0.03	0.08	0.25	-0.04	0.1	0.06

Source Tables: 14.3_4.2.2-3; 104; 103.

Table E2. Mean changes in selected chemistry parameters in the OLE-BSA phases.

	Mean changes to from OL-LI baseline to week 72 OLE-BSA		Mean changes from OL-LI to week 72 OLE-BSA			
	MTX + adalimumab N=57	Adalimumab N=46	MTX+ Placebo N=26	MTX +adalimumab N=31	Placebo N=22	Adalimumab N=24
Albumin (g/L)						
Baseline	42	42	42	42	42	42
Change	-0.1	1.8	-0.2	0	1.7	2
ALT (IU/L)						
Baseline	18	16	17	19	15	17
Change	0.9	-0.8	0	1.6(19)	-1.3	-0.4
AST (IU/L)						
Baseline	23	23	22	24*	22	23
Change	1.0	-1.0	-0.1	2(13)	-0.7	-1.3
Bicarbonate (mEq/L)						
Baseline	21	22	21	21	22	22
Change	2.0	0.6	1.9	2	0.8	0.5
Chloride (mEq/L)						
Baseline	106	105	105	106	106	105
Change	-2.1	-1.5	-2	-2	-2	-1
CPK (IU/L)						
Baseline	67	81	72	63	80	82
Change	51	22	50	51	31	13
GGT(U/L)						
Baseline	13	14	13	12	13	15
Change	-1	-2.7	-2	-0.4	-2	-3
LDH(IU/L)						
Baseline	191	177	193	188*	179	176
Change	-10	-9	-13	-8	-9	-9
Potassium (mEq/L)						
Baseline	4.3	4.4	4.3	4.2	4.4	4.3
Change	-0.03	-0.07	-0.01	-0.05	-0.1	-0.05
Sodium (mEq/L)						
Baseline	141	140	141	141	141	140
Change	-1.04	0.02	-1	-1	-0.5	0.5

Table 105, Table 14.3_4.2.1
*n=30

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