CLINICAL PHARMACOLOGY REVIEW

BLA	125057
Submission Dates	26-April, 16-August, 20-August
Generic Name	Adalimumab
Brand Name	Humira®
Indication	Treatment of juvenile rheumatoid arthritis
Sponsor	Abbott Laboratories
Dosage Form	20-mg pre-filled syringe for SC administration
Clinical Review Division	DAARP / HFD 170
PM Reviewer	Christine Garnett, Pharm.D.
CP Reviewer	Srikanth Nallani, Ph.D.
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1 EXECUTIVE SUMMARY

This supplement fulfills the postmarketing commitment (PMC) number 1 from sBLA 125057/16 for HUMIRA®, which is
"Continue study DE038, "A Multi-center, Randomized, Double-blind Placebo-Controlled Study of the safety and efficacy of human anti-TNF monoclonal antibody adalimumab in children with polyarticular juvenile rheumatoid arthritis."

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information provided in this supplement to BLA 125057. This supplement is acceptable provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the package insert.

Labeling

[redacted]

1.2 SUMMARY OF FINDINGS

1. For the treatment of juvenile rheumatoid arthritis, the sponsor has proposed a fixed-dose dosing regimen for HUMIRA. The proposed dosing regimen is HUMIRA 20-mg SC *eow* for subjects weighing less than 30 kg and HUMIRA 40-mg SC *eow* for subjects weighing 30 kg or greater. Based on the review of the pharmacokinetic and exposure-response of safety data obtained from study DE038, the fixed-dose dosing regimen with a 30-kg cut-off is acceptable.

- Of the 106 subjects in the OLE FD phase, 53 (50%) had an increase in total dose and 3 (2.8%) had a decrease in total dose when switching from HUMIRA 24-mg/m^2 to the fixed dose dosing regimen. All other subject remained on the same total daily dose of HUMIRA.
    - For the 53 subjects who had a dose increase, the median (range) dose change was +7.5-mg (+5 to +20-mg).
    - For the 3 subjects who had a dose decrease, the dose change was -5 mg.
- 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 (no methotrexate) and from 6.2 ± 4.6 μg/ml μg/ml (BSA dose) to 6.8 ± 6.9 μg/ml μg/ml (with methotrexate).
    - The mean adalimumab concentrations for the 40-mg dose are lower than those observed with BSA dose during the OL Lead-In Phase:
        - No Methotrexate: 8.1 ± 5.1 μg/ml
        - Methotrexate: 10.3 ± 5.0 μg/ml
    - The mean adalimumab concentrations for the 40-mg dose are lower than those observed with BSA dose during the OL Lead-In Phase:
        - No Methotrexate: 6.95 ± 6.2 μg/ml
        - Methotrexate: 10.6 ± 5.5 μg/ml
- For the 50 subjects who had a dose increase to 40-mg *eow*, the observed exposure to adalimumab was comparable across the weight ranges indicating that the 30-kg cut-off is appropriate (Figure 4).
- The mean exposure to adalimumab for patients with JRA is similar to the mean exposure for adult patients with RA (Table 1).

- Within the first 16-weeks of the OL Fixed-Dose Phase, 38% subjects with an increased dose experienced an infection compared to17% of subjects with same or decreased dose (Table 5).
    - There was no relationship between HUMIRA dose change and infection (Table 6).
    - There was no relationship between adalimumab exposure and infection (Table 7, Figure 7).
    - The % subjects with infection were lower than those observed in the OL Lead-In Phase (44%), in the Double-Blind Phase (60% for adalimumab, 46% for placebo), and in the OL Extension Phase (77% for adalimumab, 75% for placebo during DB phase).
- None of the subjects developed AAA after switching to the fixed dose.

2. The sponsor's PopPK model does not adequately describe the observed adalimumab data. The model under-predicts high adalimumab concentrations and over-predicts low concentrations. The median % prediction error within each quartile of observed concentrations is +98%, -5%, -23% and -34%. [redacted]

An OCP optional intra-divisional briefing was held on 13 December 2007. Briefing attendees included: Chandrahas Sahajwalla, Srikanth Nallani, Suresh Doddipaneni, Lei Zhang, Partha Roy, Joga Gobburu, Christine Garnett and Jeffrey Siegel (DAARP).

1.3 SIGNATURES

Christine Garnett, Pharm.D. Christine Garnett 12/19/2007

Srikanth Nallani, Ph.D. 12/19/2007

RD/FT Initialed by:

Joga Gobburu, Ph.D. 12/19/2007

Suresh Doddapaneni, Ph.D. 12/19/07

2 BACKGROUND INFORMATION

Adalimumab (HUMIRA®, D2E7), a recombinant, full-length immunoglobulin is the first anti-TNF monoclonal antibody that contains exclusively human sequences. Adalimumab binds to human TNF with very high affinity and specificity. Adalimumab was first approved by the Food and Drug Administration (FDA) for the treatment of subjects with rheumatoid arthritis in the US in December 2002.

Abbott Laboratories has submitted a request for labeling changes for adalimumab to add a new indication for the treatment of juvenile rheumatoid arthritis (JRA). The submission includes data from a pivotal clinical trial (DE038) which evaluated the safety, efficacy, and pharmacokinetics of adalimumab in children with polyarticular JRA.

3 QUESTION-BASED REVIEW

3.1 HOW DOES ADALIMUMAB TROUGH CONCENTRATIONS CHANGE WHEN SWITCHING FROM 24 MG/M^2 BSA TO A FIXED DOSE OF 20-MG FOR BODY WEIGHTS <30 KG AND 40-MG FOR BODY WEIGHT ≥30 KG?

The sponsor rationale for switching from a BSA dosing regimen to a fixed dose based on body weight is mainly for patient convenience and to minimize dosing errors. The sponsor selected a fixed dose of 20-mg *eow* for body weights <30 kg and 40-mg *eow* for body weights ≥30 kg because simulated trough and peak adalimumab concentrations for the fixed dose and BSA dose were comparable (<20%) across the dose regimens (Figure 8).

The fixed doses were evaluated in the OLE FD phase of study DE038. Pharmacokinetic samples were collected at baseline and predose at week 12 and 16 in subjects who had a dose change when switching from BSA to fixed dose regimen. A total of 56 subjects provided PK sample: 53 subjects had a dose increase and 3 subjects had a dose decrease (Figure 2). The overall median dose change was +7.5 mg. The median (range) dose changes for subjects weighing <30 kg (N=5) and ≥30 kg (N=50) were -5 mg (-5 to +5 mg) and +10 mg (+5 to +20-mg), respectively.

There was a trend for a proportional increase in observed adalimumab concentrations with increasing dose (Table 3, Table 4). The number of subjects who had their dose decreased was too small to draw any meaningful conclusions.

Subjects administered 40-mg *eow* had 22% mean increase in observed adalimumab concentrations when switching from a BSA to a fixed dose based on body weight. Specifically, the mean trough adalimumab concentrations increased from 5.0 μg/ml to 7.0 μg/ml (no methotrexate) and from 6.2 μg/ml to 6.8 μg/ml (with methotrexate). There were too few subjects (N=5) who received 20-mg *eow* to draw any meaningful conclusions because only 3 subjects had detectable adalimumab concentrations.

Subjects with the lowest body weights did not have higher exposure to adalimumab as shown in Figure 4.

3.2 How does exposure for JRA compare with RA?

The recommended dose of HUMIRA in adults is 40-mg SC *eow* given with or without methotrexate. With this dosing regimen the mean trough concentrations ranged between 5 μg/ml (no methotrexate) and 9 μg/ml (with methotrexate). The adalimumab exposure is comparable between patients with JRA and RA (Table 1).

The mean exposure was computed by pooling individual trough concentrations from Weeks 12/16 of the OL Lead-In Phase for subjects with no dose change with the individual trough concentrations from Week 12/16 of the OL Fixed Dose Phase for subjects with a dose change.

Table 1. Mean ± SD Adalimumab Concentrations for Patients with JRA Compared to Adult Patients with RA (Reviewer's Analysis)

JRA				RA[1]	
20-mg *eow*		40-mg *eow*		40-mg *eow*	
MTX N=6	Non-MTX N=6	MTX N=53	Non-MTX N=41	MTX	Non-MTX
10.9 ± 8.1	6.8 ± 5.5	8.1 ± 5.3	6.6 ± 6.2	8-9	5

[1] Data obtained from HUMIRA® PI

3.3 Do JRA Patients with Higher Adalimumab Exposure also Have Higher Infection Rates?

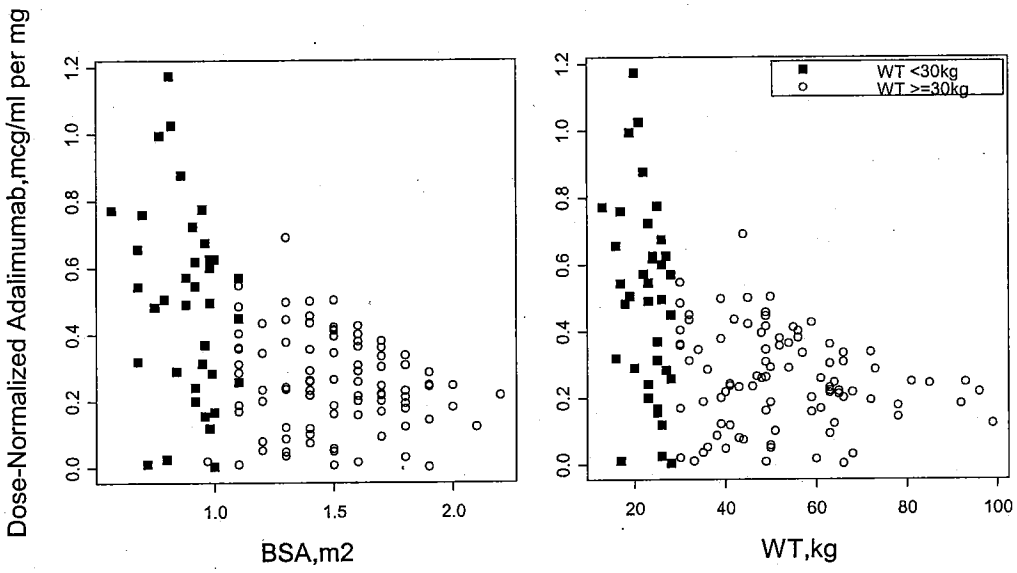
In the open-label fixed dose phase, 38% subjects who had an increased dose experienced an infection compared to 17% subjects with same/decreased dose (Table 5). To determine whether there is an exposure-response relationship for infection rate, the proportion of subjects with infection within each quartile of steady state adalimumab trough concentrations were compared. As shown in Figure 7 (OLE FD phase), there is no relationship between adalimumab exposure and infection rate.

4 Reviewer's Analysis

4.1 Comparative Exposure of the BSA and Fixed Dosing Regimens

Subjects with lower BSA or weight have higher exposures to adalimumab. Figure 1 shows the relationship between dose-normalized trough adalimumab concentrations and body size (left plot—BSA and right plot—WT).

FIGURE 1. RELATIONSHIP BETWEEN ADALIMUMAB EXPOSURE AND BODY SIZE EXPRESSED AS BSA (LEFT) OR TOTAL BODY WEIGHT (RIGHT)



The expected adalimumab trough concentrations from administering a fixed dose of HUMIRA based on body weight are comparable to the observed concentrations from a BSA dose (Table 2). The data for this table was generated by multiplying the dose-normalized observed concentration by the appropriate fixed dose based on the subject's body weight (shown as "Simulated Cτ).

TABLE 2. PROJECTED MEAN EXPOSURE WHEN SWITCHING FROM BSA TO FIXED DOSE

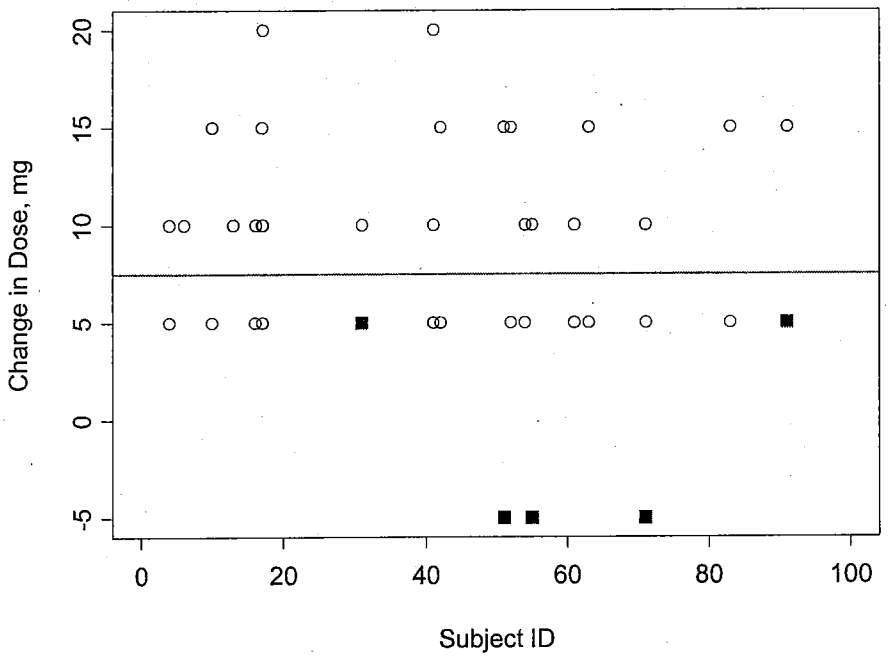
	Observed Cτ, μg/ml	Simulated Cτ, μg/ml
	24 mg/m^2 BSA Dose	Fixed Dose[1]
WT < 30 kg (N = 37)	9.1 (No MTX) 11.2 (MTX)	8.9 (No MTX) 10.6 (MTX)
WT ≥30 kg (N = 92)	7.6 (No MTX) 10.0 (MTX)	8.3 (No MTX) 11.5 (MTX)

[1]Fixed dose = 20-mg (WT<30kg) and 40-mg (WT ≥30 kg)

Upon entering the OLE FD phase, subjects who had a change in dose from their last BSA dose provided PK samples (PK Population). There were a total of 56 subjects in the PK Population: 5 received a 20-mg *eow* dose and 51 received a dose of 40-mg *eow*. Changes in total dose are visually shown in Figure 2. All subjects receiving 40-mg *eow* had an increase in dose and only five subjects receiving 20-mg *eow* had a dose change (3 with a 5 mg decrease and 2 with a 5 mg increase in dose).

FIGURE 2. REVIEWER'S ANALYSIS: CHANGE IN TOTAL DOSE FOR SUBJECTS IN THE OPEN-LABEL FIXED DOSE PHASE OF STUDY DE038 (OPEN CIRCLES = SUBJECTS

WEIGHTING ≥30 KG, CLOSED SQUARES = SUBJECTS WEIGHING <30 KG, RED LINE = MEDIAN DOSE CHANGE)



Despite the small sample size and large between subject variability, there appears to be a proportional increase in mean adalimumab concentrations when switching from BSA to the 40-mg fixed-dose dosing regimens (Table 3). There are too few subjects in the 20-mg fixed-dose group to draw any conclusions. Individual concentration-time data stratified by dose change are shown in Figure 3.

TABLE 3. MEAN ADALIMUMAB CONCENTRATIONS BY DOSE CHANGE FOR ALL SUBJECTS (REVIEWER'S ANALYSIS)

Dose		Dose Change	N	Mean ± SD Adalimumab Cτ, μg/ml		
BSA Dose	Fixed Dose			0 Weeks	12 Weeks	16 Weeks
25-mg	20-mg	-5-mg	3	0.047	0.343	0.753
15-mg	20-mg	+5-mg	2	5.9 (MTX)	7.8 (MTX)	9.9 (MTX)
20-mg	40-mg	+ 20-mg	2	NA	NA	NA
25-mg	40-mg	+ 15-mg	10	7.8 ± 4.5 7.9 (MTX) 7.7 (No MTX)	11.9 ± 8.9 16.8 (MTX) 9.5 (No MTX)	11.1 ± 6.7 13.0 (MTX) 10.2 (No MTX)
30-mg	40-mg	+ 10-mg	16	4.6 ± 4.2 5.9 (MTX)	5.4 ± 5.4 7.0 (MTX)	5.8 ± 5.5 7.3 (MTX)

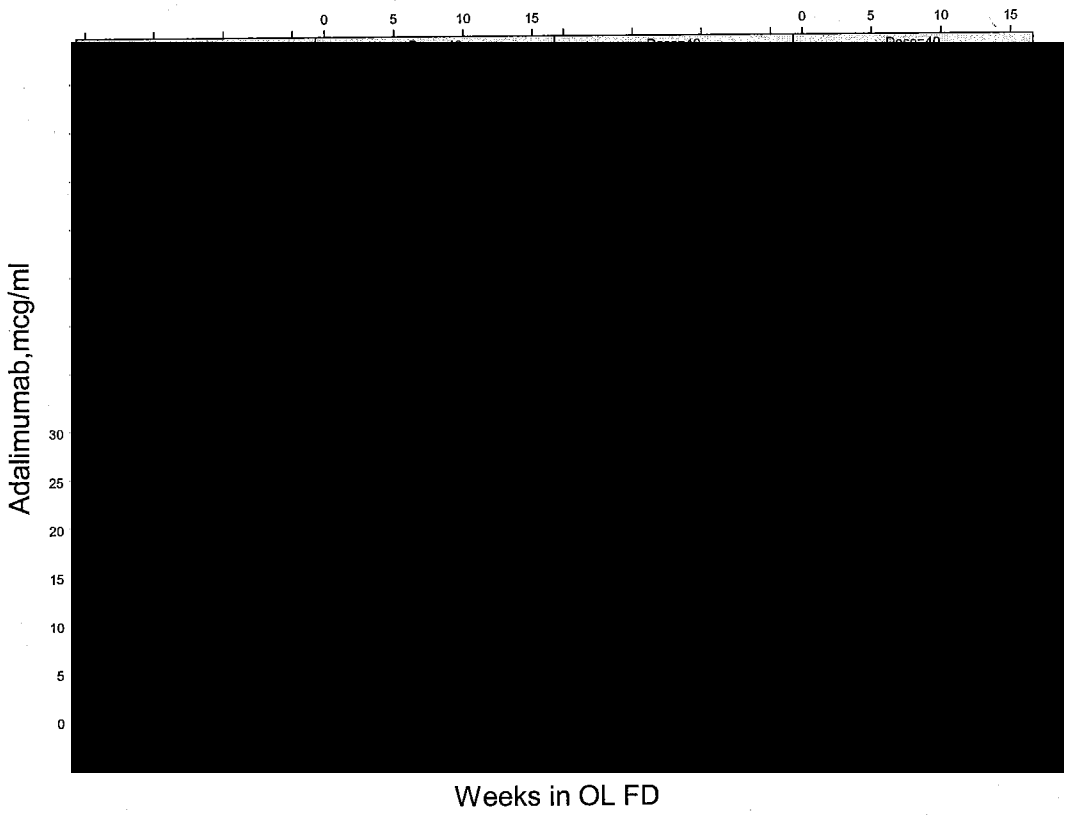
				2.9 (No MTX)	3.4 (No MTX)	4.0 (No MTX)
35-mg	40-mg	+ 5-mg	23	5.9 ± 5.4 6.4 (MTX) 4.8 (No MTX)	6.4 ± 5.9 6.5 (MTX) 6.2 (No MTX)	6.3 ± 5.3 5.8 (MTX) 7.4 (No MTX)

NA = no data available

TABLE 4. MEAN ADALIMUMAB CONCENTRATIONS BY DOSE CHANGE FOR AAA-NEGATIVE SUBJECTS (REVIEWER'S ANALYSIS)

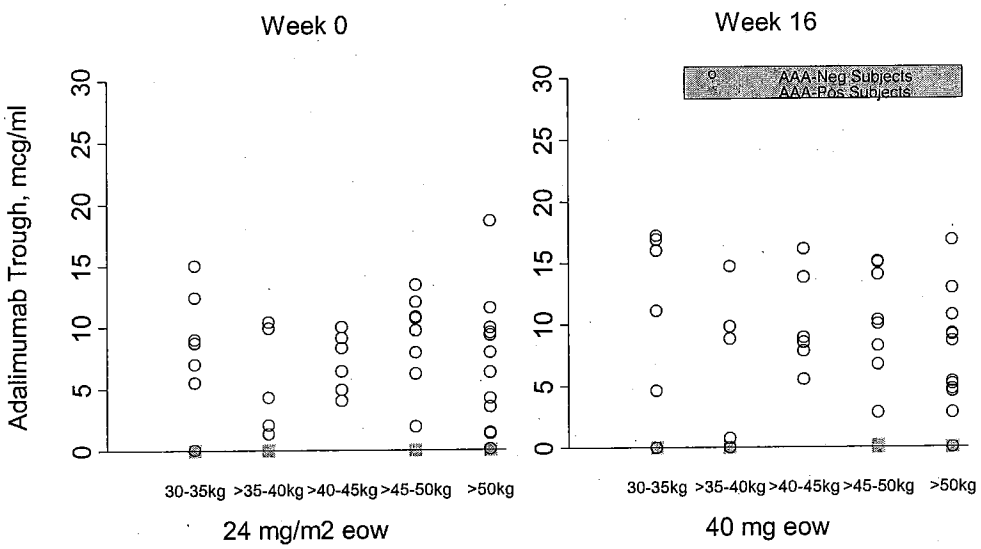
Dose		Dose Change	N	Mean ± SD Adalimumab Cτ, μg/ml		
BSA Dose	Fixed Dose			0 Weeks	12 Weeks	16 Weeks
25-mg	20-mg	-5-mg	2	0.070	0.515	1.13
15-mg	20-mg	+5-mg	2	5.9 (MTX)	7.8 (MTX)	9.9 (MTX)
20-mg	40-mg	+ 20-mg	2	NA	NA	NA
25-mg	40-mg	+ 15-mg	9	8.6 ± 3.8 7.9 (MTX) 9.0 (No MTX)	13.4 ± 8.2 16.8 (MTX) 11.3 (No MTX)	12.6 ± 5.6 13.0 (MTX) 12.3 (No MTX)
30-mg	40-mg	+ 10-mg	12	6.3 ± 3.5 5.9 (MTX) 8.6 (No MTX)	7.2 ± 5.0 7.0 (MTX) 8.0 (No MTX)	7.8 ± 4.9 7.3 (MTX) 9.2 (No MTX)
35 mg	40-mg	+ 5 mg	19	7.2 ± 5.2 7.4 (MTX) 6.9 (No MTX)	7.3 ± 5.9 7.2 (MTX) 7.5 (No MTX)	7.3 ± 5.1 6.7 (MTX) 8.9 (No MTX)

FIGURE 3. INDIVIDUAL SERUM ADALIMUMAB CONCENTRATION-TIME DATA STRATIFIED BY DOSE CHANGE (REVIEWER'S ANALYSIS)



When switching from the BSA to the fixed dose dosing regimen, subjects with the lowest body weights (30-35 kg) do not have higher exposure to adalimumab compared to subjects with higher body weights (>50 kg) as shown in Figure 4.

FIGURE 4. TROUGH ADALIMUMAB CONCENTRATIONS BY WEIGHT GROUP AND DOSING REGIMEN



4.2 ADALIMUMAB EXPOSURE IN AAA-POSITIVE SUBJECTS

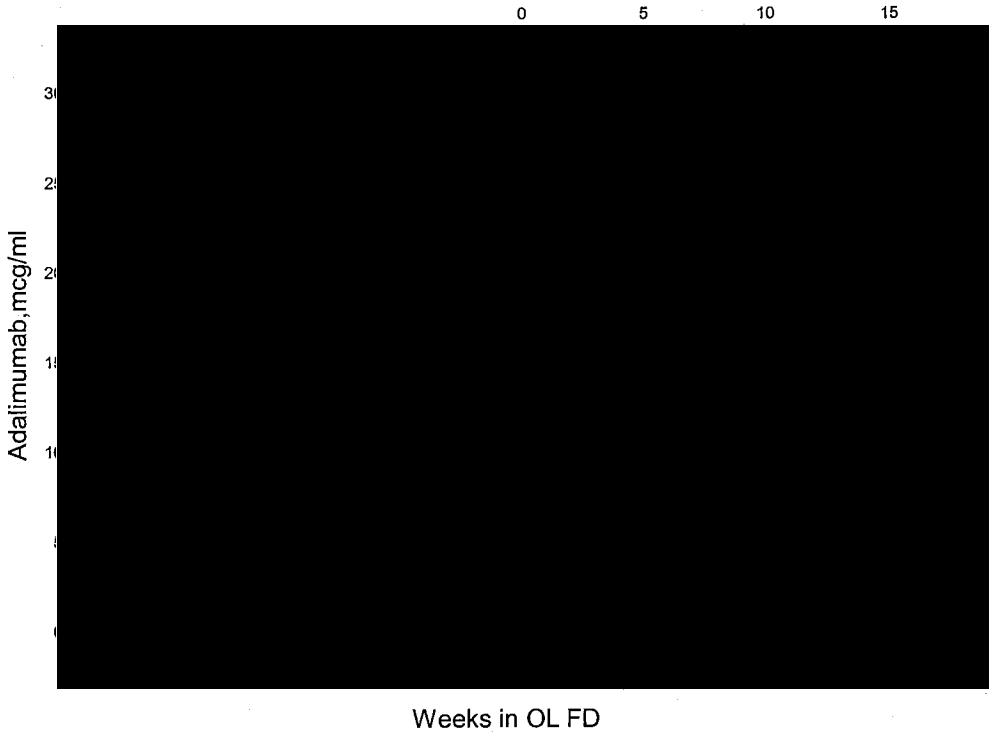
Twenty-seven subjects (27/171, 15.8%) with JRA had at least one AAA positive sample on treatment sample during the OLLI and DB phases. The percentage of AAA positive subjects was 5.9% in the MTX treatment group and 25.6% in the group not taking MTX.

FIGURE 5. INDIVIDUAL SERUM ADALIMUMAB CONCENTRATION-TIME DATA FOR 27 AAA-POSITIVE SUBJECTS

For the 56 subjects included in the pharmacokinetic analyses from the OLE FD phase, 12 subjects (21.4%) were identified as AAA positive during study DE038. None of the subjects developed AAA after switching to the fixed dose.

For the 12 subjects who were AAA-positive, the majority of adalimumab concentrations were BLQ as shown in Figure 6.

FIGURE 6. INDIVIDUAL SERUM ADALIMUMAB CONCENTRATION-TIME DATA STRATIFIED BY IMMUNOGENICITY (REVIEWER'S ANALYSIS)



4.3 EXPOSURE-RESPONSE ANALYSIS FOR INFECTION

The number (%) of ITT subjects with an infection was higher in subjects who had an increased dose compared to subjects with same/decreased dose during the first 16 weeks (Table 5).

TABLE 5. NUMBER (%) SUBJECTS WITH INFECTIONS IN THE OLE FD PHASE BY DOSE CHANGE (REVIEWER'S ANALYSIS)

	ITT Population		PK Population	
	Same/Decreased Dose N=53	Increased Dose N=53	Same/Decreased Dose N=3	Increased Dose N=53
Infections	9 (17%)	20 (38%)	3 (100%)	19 (36%)

(Sponsor's Table 71 in DE038 Through Week 16 Fixed Dose Interim Clinical Study Report, page 330 and Sponsor's Table 8 in DE038 Pharmacokinetic Report – Open-Label Extension, page 64)

Exploratory graphics were performed to characterize the exposure-response relationship for infection in the OLE FD phase of the study. The data sets used for this analysis was obtained from the sponsor:

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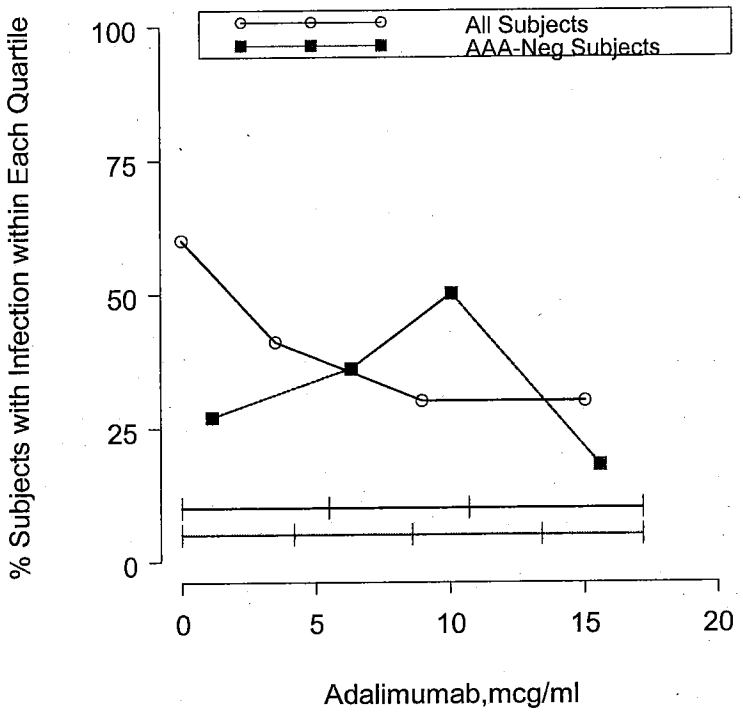
As shown in Figure 7, subjects in the PK population with lowest concentrations had the highest infection rate. This finding is inconsistent with the results of the ITT population where more subjects with an increase in dose had infection (Table 2). Of the 10 AAA-positive subjects who had one post-dosing PK sample, 8 had an infection during the OLE FD phase. When only AAA-negative subjects were considered, there was no relationship between exposure and infections. There was also no difference in the proportion of subjects with infection within each quartile with methotrexate use. The major imitation of this analysis is only subjects with increase/decreased dose change provided PK information (Table 5). PK data was not obtained in patients who remained on the same dose during the OLE FD phase.

FIGURE 7. PROPORTION OF SUBJECTS IN THE PK POPULATION OF THE OLE FD PHASE WITH INFECTION BY QUARTILES OF STEADY STATE ADALIMUMAB CONCENTRATIONS (REVIEWER'S ANALYSIS)



The reviewer's exposure-response analysis for infection is consistent with the sponsor's safety evaluation for the ITT population. Table 6 shows there is no dose response relationship for infections. Table 7 and Table 8 shows that there is no exposure (dose/WT) response relationship for infections.

TABLE 6. TEAEs BY DOSE INCREASE (ITT POPULATION, 16-WEEK DATA)

	MTX				non-MTX				Overall			
	Increased				Increased				Increased			
	5 mg N = 18	10 mg N = 9	>10 mg N = 4	Total N = 31	5 mg N = 7	10 mg N = 7	>10 mg N = 8	Total N = 22	5 mg N = 25	10 mg N = 16	>10 mg N = 12	Total N = 53
Med DRA Preferred Term	n (%)											
Any adverse event	11 (61.1)	4 (44.4)	4 (100.0)	19 (61.3)	6 (85.7)	6 (85.7)	5 (62.5)	17 (77.3)	17 (68.0)	10 (62.5)	9 (75.0)	36 (67.9)
At least possibly related to drug	4 (22.2)	0	1 (25.0)	5 (16.1)	2 (28.6)	3 (42.9)	3 (37.5)	8 (36.4)	6 (24.0)	3 (18.8)	4 (33.3)	13 (24.5)
Severe adverse event	1 (5.6)	0	0	1 (3.2)	1 (14.3)	1 (14.3)	0	2 (9.1)	2 (8.0)	1 (6.3)	0	3 (5.7)
Serious adverse event	0	0	0	0	0	1 (14.3)	0	1 (4.5)	0	1 (6.3)	0	1 (1.9)
Leading to discontinuation of study drug	0	0	0	0	0	0	0	0	0	0	0	0
At least possibly related to drug SAE	0	0	0	0	0	0	0	0	0	0	0	0
Infections	6 (33.3)	3 (33.3)	2 (50.0)	11 (3.5)	4 (57.1)	4 (57.1)	1 (12.5)	9 (40.9)	10 (40.0)	7 (43.8)	3 (25.0)	20 (37.7)
Serious infections	0	0	0	0	0	1 (14.3)	0	1 (4.5)	0	1 (6.3)	0	1 (1.9)
Malignancies	0	0	0	0	0	0	0	0	0	0	0	0
Injection site reactions	1 (5.6)	0	1 (25.0)	2 (6.5)	0	1 (14.3)	2 (25.0)	3 (13.6)	1 (4.0)	1 (6.3)	3 (25.0)	5 (9.4)
Opportunistic Infections	0	0	0	0	0	0	0	0	0	0	0	0
Congestive heart failure related	0	0	0	0	0	0	0	0	0	0	0	0
Demyelinating disease	0	0	0	0	0	0	0	0	0	0	0	0
Hepatic-related adverse event	1(5.6)	0	0	1 (3.2)	0	0	0	0	1 (4.0)	0	0	1 (1.9)
Allergic reaction related	0	0	0	0	0	1 (14.3)	0	1 (4.5)	0	1 (6.3)	0	1 (1.9)
Lupus-like syndrome	0	0	0	0	0	0	0	0	0	0	0	0

(Sponsor's Table 72 in DE038 Through Week 16 Fixed Dose Interim Clinical Study Report, page 332)

TABLE 7. TEAEs BY BASELINE WEIGHT-ADJUSTED DOSE (MG/KG) PERCENTILE (ITT POPULATION, 16-WEEK DATA)

	Min -< P5	P5 - <P25	P25- <P50	P50 < P75	P75 -< P95	P95 – Max
	N = 5	N = 23	N = 25	N = 26	N = 21	N = 6
	n (%)					
Any AE	3 (60.0)	10 (43.5)	13 (52.0)	18 (69.2)	13 (61.9)	4 (66.7)
At least possibly related to drug	1 (20.0)	1 (4.3)	3 (12.0)	7 (26.9)	5 (23.8)	1 (16.7)
Severe AE	0	1 (4.3)	0	1 (3.8)	2 (9.5)	0
Serious AE	1 (20.0)	1 (4.3)	0	0	1 (4.8)	0
Leading to discontinuation of study drug	0	0	0	1 (3.8)	0	0
At least possibly related to drug SAE	0	0	0	0	0	0
Infections	1(20.0)	5 (21.7)	7 (28.0)	8 (30.8)	6 (28.6)	2 (33.3)
Serious infections	0	0	0	0	1 (4.8)	0
Malignancies	0	0	0	0	0	0
Injection site reactions	0	0	1 (4.0)	2 (7.7)	3 (14.3)	0

(Sponsor's Table 72 in DE038 Through Week 16 Fixed Dose Interim Clinical Study Report, page 332)

TABLE 8. AEs BY BASELINE WEIGHT (ITT POPULATION, 16-WEEK DATA, REVIEWER'S ANALYSIS)

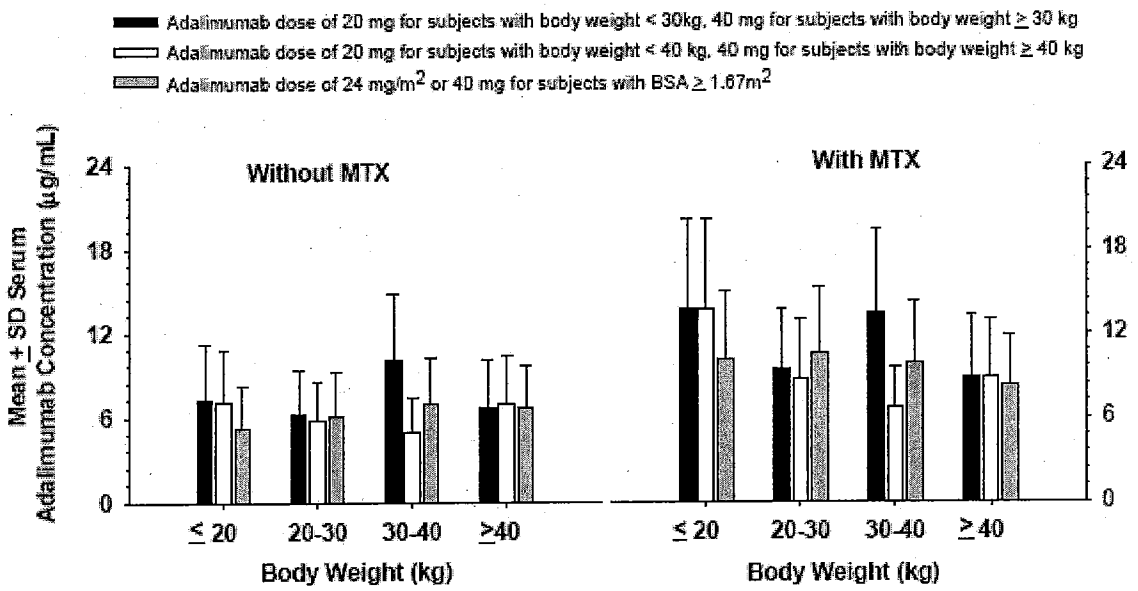
AE	20-mg *eow*	40-mg *eow*				
	20-<30kg (0.69-1)[1]	30-35kg (1.16-1.3)	>35-40kg (1-1.11)	>40-45kg (0.90-0.99)	>45-50kg (0.8-0.88)	>50kg (0.37-0.79)
	N=12	N=11	N=8	N=6	N=12	N=57
Any	7 (58.3)	8 (72.7)	7 (87.5)	1 (16.7)	10 (83.3)	28 (49.1)
Infection	4 (33.3)	4 (36.4)	3 (37.5)	1 (16.7)	5 (41.7)	12 (21.1)
Injection	0	1 (9.1)	2 (25.0)	0	0	3 (5.3)

5 SPONSOR'S JUSTIFICATION FOR THE FIXED-DOSE OF 20-MG FOR BODY WEIGHTS <30 KG AND 40-MG FOR BODY WEIGHTS ≥30 KG

The sponsor used a modeling and simulation approach to identify the fixed dose to administer to subjects with JRA. The sponsor considered two dosing regimens: 1) 20-mg of adalimumab *sc eow* for subjects with body weight < 30 kg and 40-mg *sc eow* for subjects with body weight ≥30 kg; 2) 20-mg *sc eow* for subjects with body weight < 40 kg and 40-mg *sc eow* for subjects with body weight ≥40 kg. For the BSA dose regimen, adalimumab at 24 mg/m2 of BSA (up to a maximum of 40-mg total body dose) was given *sc eow*

The mean and standard deviation of the simulated Week 16 pre-dose serum adalimumab concentrations by body weight and dosing regimen are plotted in Figure 8. The sponsor concluded that the fixed dose regimen with 40 kg cut-off produced lower adalimumab concentrations compared to the BSA regimen. Therefore, the 30 kg cut-off was selected for the OLE FD phase.

FIGURE 8. SPONSOR'S FIGURE: MEAN SIMULATED WEEK 16 TROUGH ADALIMUMAB CONCENTRATIONS BY BODY WEIGHT AND DOSING REGIMEN



6 SPONSOR'S EVALUATION OF THE FIXED DOSE REGIMEN

6.1 OBJECTIVES

Modeling objectives were:

- to estimate adalimumab population pharmacokinetic parameters in pediatric subjects (at least 4 years old) with polyarticular JRA
- to compare the pharmacokinetics of *eow* fixed dosing based on body weight to the *eow* variable dosing based on BSA

6.2 CLINICAL TRIAL DESIGN

DE038 was a multicenter, Phase 3, randomized, stratified, double blind, parallel-group study in children (ages of 4 to 17 years) with polyarticular JRA. A schematic of the study design is shown in Figure 9.

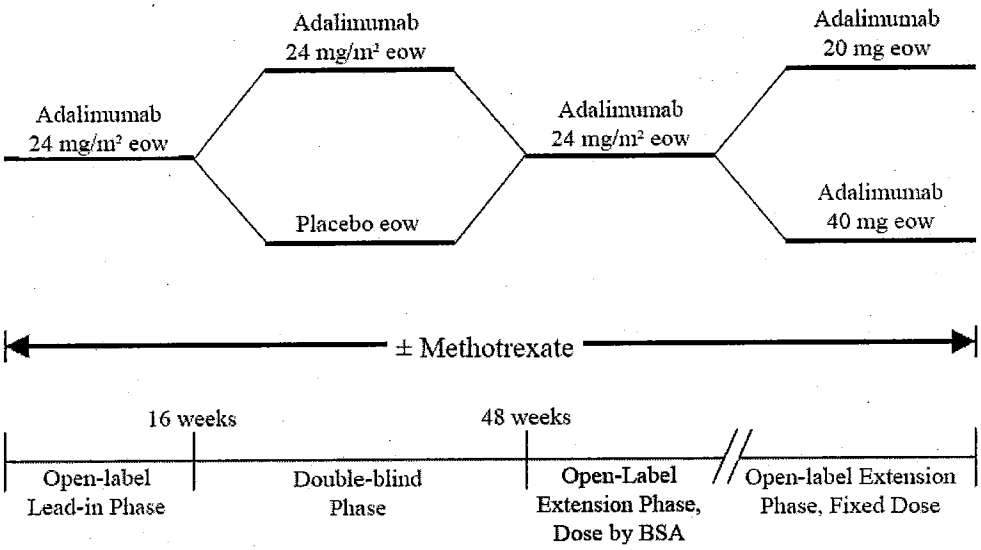
Open-Label Lead-In (OL IN): All subjects received adalimumab at 24 mg/m2 BSA (up to a maximum of 40-mg total body dose) *sc eow*.

Double Blind (Randomized Withdrawal, DB): Subjects who responded to open-label treatment were eligible to be randomized in a 1:1 ratio to placebo or adalimumab treatment arms in the DB phase. Subjects were monitored for disease flare during the DB phase of the study.

Open-Label Extension BSA (OLE BSA): Subjects who experienced disease flare during the DB phase were eligible to immediately enroll into the OLE phase without completing the entire 32 weeks. These subjects, along with the subjects who completed the entire 32-weeks in the DB phase participated in the OLE BSA dosing regimen.

Open Label Extension Fixed Dose (OLE FD): Subjects weighing less than 30 kg were given 20-mg of adalimumab *eow sc* and subjects weighing 30 kg or more were given 40-mg of adalimumab *eow sc*.

FIGURE 9. SCHEMATIC OF THE STUDY DESIGN FOR DE038



(Sponsor's Figure 1 in DE038 Pharmacokinetic Report – Open-Label Extension, page 37)

6.3 DATA AND DATA EDITING

All subjects enrolled in Study DE038 (N = 171) were included in the NONMEM analyses (Table 9). A total of 1001 data points were used.

TABLE 9. REVIEWER'S TABLE: DATA USED IN POPPK ANALYSIS

Study Phase	Number of Subjects	Dose	PK Sampling Times
OL LI	171	24 mg/m^2	Even Numbered Subjects: Baseline, Weeks 1, 2, 8, 16, 24, 32, 40, and 48 Odd Numbered Subjects: Baseline, Weeks 1, 2, 4, 12, 20, 28, 36, and 44
DB	133	24 mg/m^2	
OL BSA	128	24 mg/m^2	None Collected
OL FD	56 (5 received 20-mg and 51 received 40-mg)	20-mg for WT<30 kg 40-mg for WT ≥30kg	Baseline and at Weeks 12, 16 and at early termination

6.4 BIOANALYTICAL ASSAYS

6.4.1 Adalimumab Samples

Serum adalimumab concentrations were measured by ELISA. The assay has a limit of quantification of 2.5 ng/ml diluted serum. The assay is both accurate (88% to 111% of the expected concentration range of 2.5 to 40 ng/ml) and precise (CV 3.9% to 5.2%).

Only free, non-complexed adalimumab were detected. Adalimumab bound to TNF-α or neutralizing anti-adalimumab antibodies was not detected.

6.4.2 AAA Samples

Serum samples were analyzed for AAA using a validated [redacted] immunoassay.

[redacted]

6.5 RESULTS

6.5.1 Model and Model Selection

6.5.1.1 Base PopPK Model

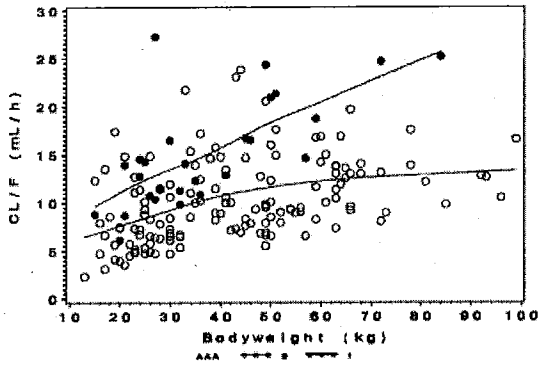
A one-compartment model parameterized with CL/F, V/F, and Ka was used to describe the adalimumab concentration-time data. Between-subject random effects for CL/F and V/F were described using exponential models and residual error was described using a proportional error.

6.5.1.2 Covariate Model Selection

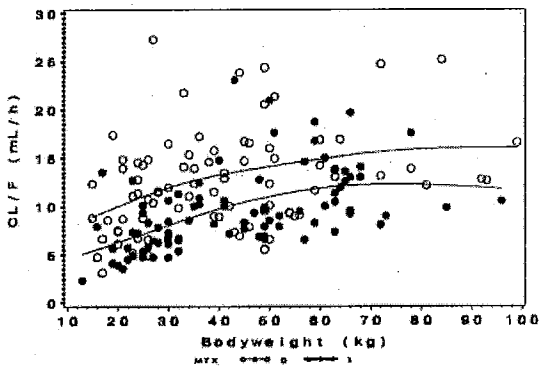
Body weight, MTX comedication, presence of AAA, age, Tanner Stage, creatinine clearance, creatinine levels, and height were identified as significant univariate contributors to the observed variability of adalimumab CL/F, and body weight, height, and age were identified as significant univariate contributors to the observed variability of adalimumab V/F.

After multiple stepwise inclusion and backward exclusion steps as well as visual inspection of the goodness of the obtained model results, the effect of MTX comedication, AAA presence, and body weight on CL/F and body weight on V/F were identified as significant covariates for the final model. The relationship between CL/F and these covariates are presented in Figure 10.

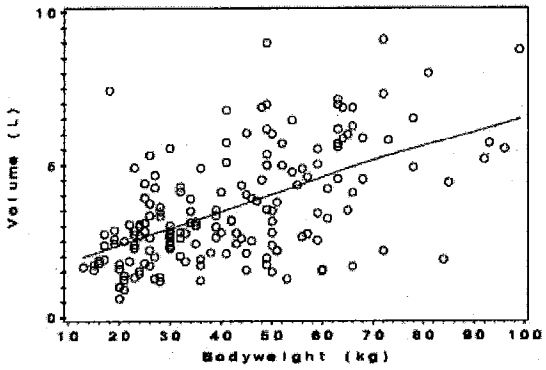
FIGURE 10. SPONSOR'S FIGURE: SIGNIFICANT COVARIATES VS. PK PARAMETERS



Solid circle: AAA positive; Open circle: AAA negative



Solid circle: w/ MTX; Open circle: w/o MTX



(Sponsor's Appendix 15.4-2.2, pages 551, 553)

6.5.1.3 Final PopPK Model

6.5.1.3.1 Model Description

The NM-Tran control stream for the Final Model (Model 47) is located in the Appendix.

6.5.1.3.2 Parameter Estimation Results

TABLE 10. FINAL PARAMETERS FOR ADALIMUMAB (MODEL 47)

Parameter (unit)		Estimate (% RSE)
Structural model parameters		
CL/F (L/day)	= (THETA(2)	0.011 (31.8)
	* (1-AAA)*WT**THETA(5)	0.786 (10.6)
	+ THETA(2)	
	* AAA*WT**THETA(6))	0.962 (8.9)
	+ THETA(7) * (1-MTX)	0.0633 (26.7)
V/F (L)	= THETA(3)	3.58 (8.2)
	+ THETA (4)*(WT-40)	0.0942 (10.2)
K_a (1/day)	= THETA(1)	0.278 (19.9)
Inter-individual variability parameters		
%CV^ for CL/F		36.3
%CV^ for V/F		40.1
Residual error parameters		
% CV (Proportional component)		58.1

Cross Reference: Appendix 15.4__1.6

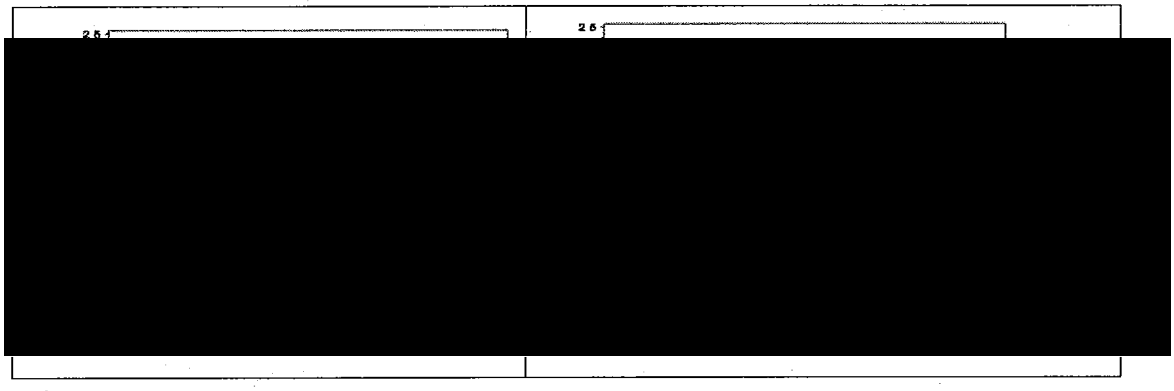
^ CV = an approximation of the coefficient of variation of inter-individual variability.

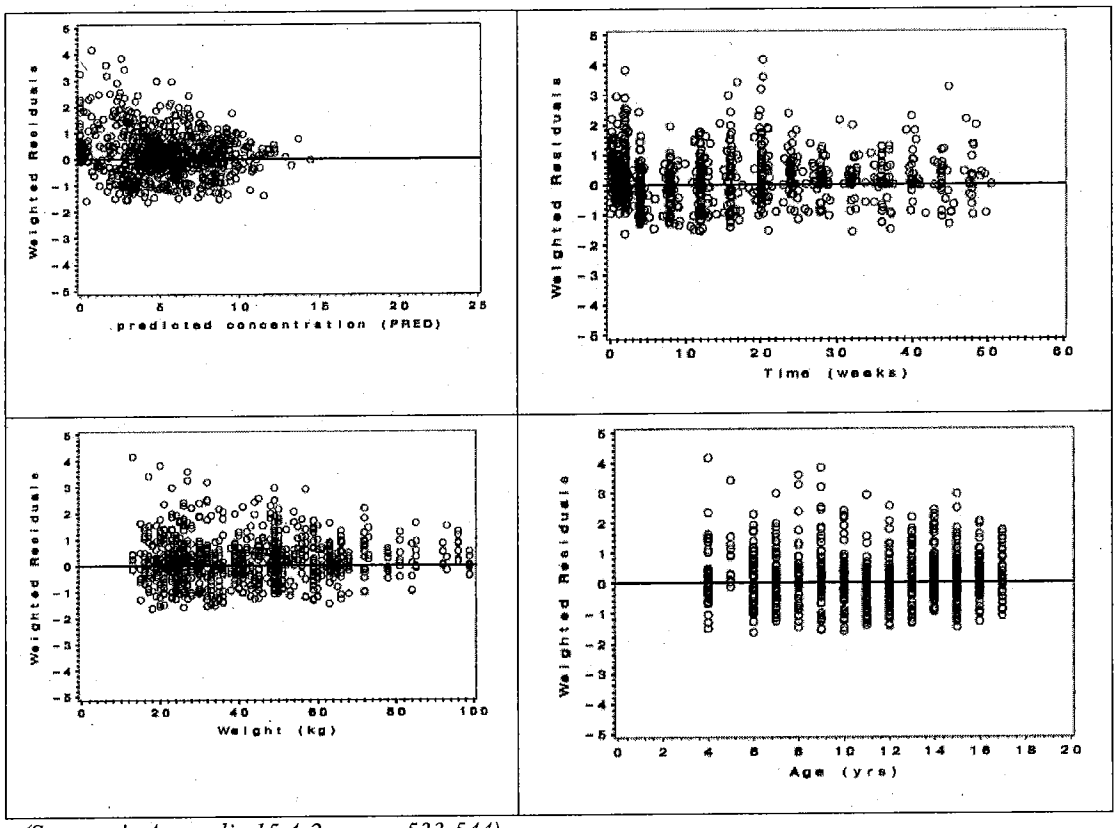
%RSE = 100 • SE / Estimate.

(Sponsor's Table 22, page 82)

6.5.1.3.3 Goodness of Fit Plots

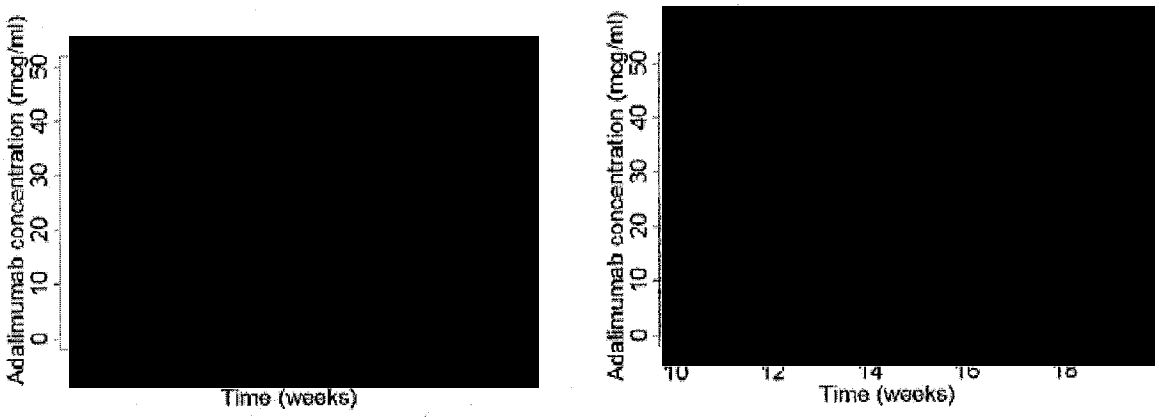
FIGURE 11. OBSERVED CONCENTRATIONS VS. POPULATION AND INDIVIDUAL PREDICTIONS FOR FINAL MODEL (MODEL 47)





(Sponsor's Appendix 15.4-2, pages 533-544)

FIGURE 12. OBSERVED VS. SIMULATED SERUM ADALIMUMAB CONCENTRATIONS IN SUBJECTS RECEIVING BSA DOSE REGIMEN OR FIXED DOSE REGIMEN



(Sponsor's Figure 9, page 88)

6.5.1.4 Model-Based Simulations Using the Pharsight Trial Simulator

A total of 5000 subjects were simulated for each regimen, assuming 100% dosing compliance. The model structure and the parameter estimates from the final population pharmacokinetic model (Table 10) were used. Distribution of body weight except the lowest body weight was assumed to be the same as that observed at the baseline of OL-LI phase.

Summary statistics for the trough and peak serum adalimumab concentrations at steady state are listed in Table 11. The mean and median of both trough and peak serum concentrations were slightly higher (ranging from 9.01% to 12.71%) with fixed dosing than with BSA dosing.

When the concentrations are stratified by body weight as listed in Table 12, the mean simulated concentrations for the fixed dose regimen are within 20% of the BSA dose except for subjects weighing between 30 and 40 kg. For these subjects, the mean simulated adalimumab concentrations are 40% higher.

TABLE 11. SUMMARY OF SIMULATED TROUGH AND PEAK CONCENTRATIONS AT STEADY STATE BY DOSING REGIMEN

				Percentiles				
		Mean	SD	5th	25th	Median	75th	95th
Trough	FD	8.14	4.89	2.01	4.60	7.19	10.65	17.30
	BSA	7.22	3.96	1.97	4.27	6.60	9.51	14.77
	%Diff*	12.71		1.60	7.53	9.01	12.02	17.11
Peak	FD	12.22	5.36	5.35	8.39	11.31	15.05	22.08
	BSA	10.89	4.15	5.21	7.86	10.29	13.32	18.77
	%Diff*	12.21		2.61	6.69	9.88	13.01	17.65

* %Diff, the percentage of difference between FD and BSA; calculated as %Diff=(FD-BSA)/BSA×100%

BSA: BSA Dose

FD: Fixed Dose

(Sponsor's Table 33, pages 100)

TABLE 12. SUMMARY OF SIMULATED TROUGH AND PEAK CONCENTRATIONS AT STEADY STATE BY BODY WEIGHT

		Trough			Peak		
		Mean	SD	Median	Mean	SD	Median
Between 15 and 20 kg	FD	8.21	5.32	7.17	13.66	5.53	12.39
	BSA	6.92	4.41	6.04	11.78	4.49	11.52
	%Diff*	18.75		18.67	15.89		7.52
Between 20 and 30 kg	FD	6.32	3.68	5.61	10.04	3.80	9.38
	BSA	7.36	4.28	6.49	11.73	4.42	10.93
	%Diff*	-14.14		-13.59	-14.43		-14.12
Between 30 and 40 kg	FD	10.35	5.93	9.32	15.72	6.08	14.85
	BSA	7.46	3.96	6.91	11.28	4.07	10.75
	%Diff*	38.72		34.99	39.34		38.09
Between 40 and 50 kg	FD	8.88	4.69	8.12	12.99	4.81	12.39
	BSA	7.40	3.95	6.83	10.82	4.02	10.27
	%Diff*	19.92		18.82	20.01		20.71
Above 50 kg	FD	7.15	3.75	6.56	10.03	3.96	9.58
	BSA	6.80	3.48	6.38	9.59	3.64	9.11
	%Diff*	5.06		2.93	4.53		5.16

* %Diff, the percentage of difference between FD and BSA; calculated as %Diff=(FD-BSA)/BSA×100%

FD: Fixed Dose

BSA: BSA Normalized Dose

(Sponsor's Table 32, pages 99)

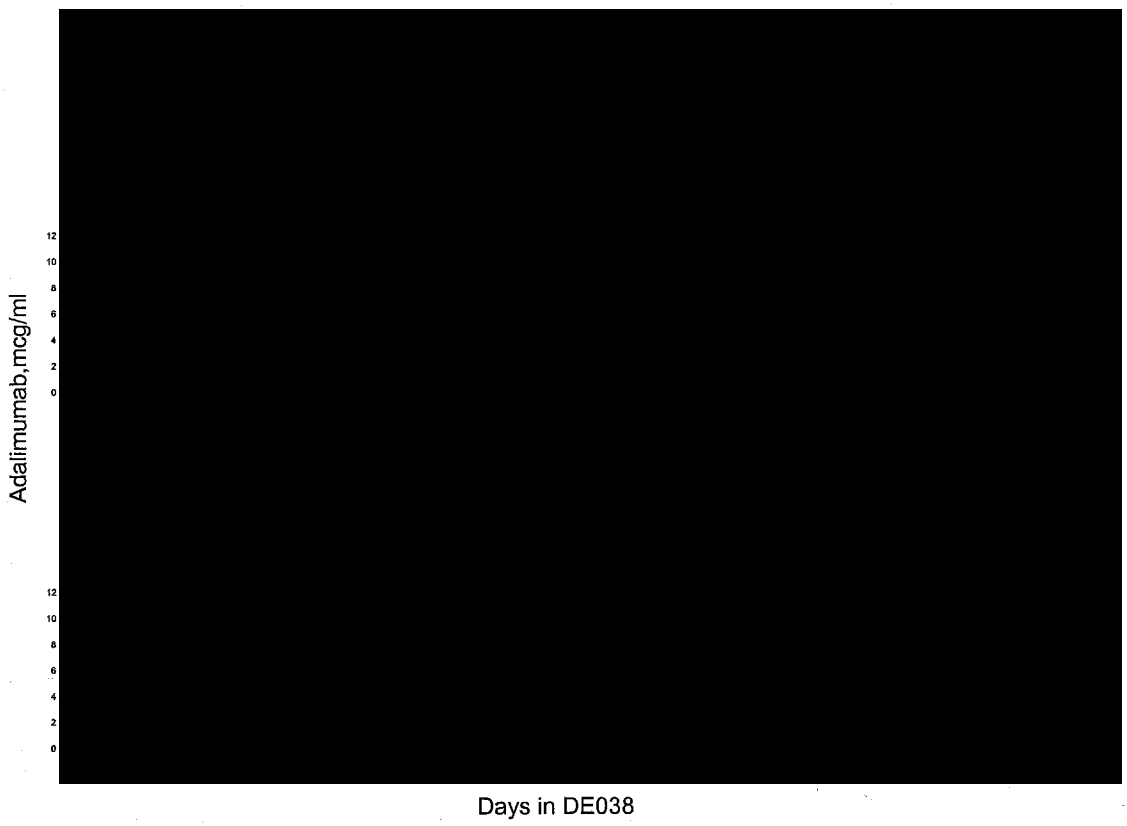
6.6 REVIEWER'S COMMENTS ON SPONSOR'S ANALYSIS

1. The sponsor's PopPK model had the following deficiencies:
   - The sponsor's model did not take into account time-varying CL/F. There were 27 subjects who developed AAA which resulted in increased CL/F (Figure 5). Instead, the sponsor's model allowed development of AAA to influence the relationship between body weight and CL/F (Table 10).
   - Diagnostic plots of the sponsor's final PK model (model 47) show poor fitting to the observed data (Figure 11). The model underpredicts high adalimumab concentrations. The median % prediction error within each quartile of observed concentrations is +98%, -5%, -23% and -34%.

Quartile of Observed Concentrations	Range of Observed Concentrations	Median %PE	Mean %PE
1	[redacted]	93.5	52.3
2	[redacted]	-4.98	-11.4

3	[redacted]	-22.5	-25.3
4	[redacted]	-33.9	-35.3

- Simulations from the PopPK model showed poor correlation with the observed data (Figure 12). There is a trend for the model to overestimate the observed data since there is only 1 observed value greater than the 95th percentile. Observed concentrations lower than the 5th percentile were attributed to AAA-positive subjects.
- The concentrations obtained from AAA-positive subjects are lower than the LLQ as shown in the figure below. These BLQ concentrations do not provide information for the estimation of CL/F and could have been removed. These BLQ concentrations attributed to the poor model fits.



7 APPENDIX 1: NM-TRAN FOR POPPK MODEL