

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
sBLA 125057/110

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

BLA:	125057
Brand Name:	Humira
Generic Name:	Adalimumab
Dosage form and Strength:	Injectable solution in a single-use, 1 mL pre-filled glass syringe or a single-use, pre-filled pen (Humira Pen), providing 40 mg (0.8 mL)
Route of administration:	Subcutaneous Injection
Indication:	Moderate to Severe Chronic Plaque Psoriasis
Proposed dosing regimen:	80 mg given as an initial dose at Week 0 and 40 mg given every other week as maintenance doses starting Week 1
Sponsor:	Abbott
Type of submission:	Efficacy Supplement (110)
Clinical Division:	Division of Dermatology and Dental Products (HFD-540)
OCP Division:	DCP III
Priority:	Standard
Submission date:	03/23/07
Reviewer:	Tien-Mien Chen, Ph.D.
Team Leader:	Sue-Chih Lee, Ph.D.

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1. Executive Summary

1.1 Recommendations

BLA125057/110, an efficacy supplement of Humira (adalimumab) for subcutaneous (SC) Injection for the indication of treating patients with moderate to severe chronic plaque psoriasis (CPP) has been reviewed by the Office of Clinical Pharmacology (OCP). From the OCP perspective, the clinical pharmacology section of this efficacy supplement of Humira (sBLA125057/110) is acceptable. The labeling comment (p.18) should be conveyed to the sponsor.

1.2 Phase IV Commitments:

b(4)

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background:

Adalimumab is a recombinant human immunoglobulin (IgG₁) monoclonal antibody containing only human peptide sequences. Abbott's Humira (adalimumab) for SC injection was first approved by the Agency in 2002 for reducing signs and symptoms in adult patients with active rheumatoid arthritis (RA) and later in patients with active psoriatic arthritis (PsA) and in patients with active ankylosing spondylitis (AS). The efficacy supplement (sBLA125057/89) approved in early 2007 was for patients with moderate to severe Crohn's Disease (CD).

A new efficacy supplement, sBLA125057/110, was submitted on 03/23/07 seeking approval for patients with moderate to severe CPP, the subject of this clinical pharmacology review. The proposed SC dosing regimen is 80 mg given on Week 0 as an initial dose and then 40 mg every other week (EOW) starting from Week 1 as maintenance doses.

Overview of Clinical Pharmacology and Biopharmaceutics:

A Phase-2 double-blind, placebo-controlled trial (M02-528) and two Phase-3 double-blind placebo-controlled trials (M03-656 and M04-716) were the pivotal trials for supporting the current application of adalimumab for the treatment of moderate to severe CPP. All their extension studies were also submitted to support the efficacy and/or safety of the product.

The clinical pharmacology information on adalimumab, including PK, dose-response and immunogenicity, in the CPP patient population was primarily obtained from Study M02-528 and M03-656. No PK data was collected from M04-716. The sponsor also conducted a population PK (PPK) analysis to estimate the adalimumab PK parameters in this target patient population using data from Studies M02-528 and M03-656. However,

⌋ The currently approved vials or pre-filled syringes (40 mg/0.8 mL) of Humira were used in the clinical trials for CPP. Therefore, no comparability studies were necessary.

b(4)

Study M02-528 was a 12-week, randomized, double blind, placebo-controlled, multicenter, Phase-2 efficacy and safety study (N=148). In addition to the proposed dosing regimen (Regimen A), a higher maintenance dosing regimen (40 mg every week; Regimens B) was also employed in Study M02-528 for studying the exposure-response relationships. Patients were randomly assigned to one of three groups (two active treatment groups and placebo).

Study M03-656 was a short- and long-term, multi-center, Phase-3 efficacy and safety study. This study consisted of three treatment periods, Period A (16 weeks; N=1212), Period B (17 weeks; N=606), and Period C (19 weeks; N=490). The proposed dosing regimen was employed.

Study M04-716, a third placebo-controlled confirmatory Phase-3 trial in patients with psoriasis (N=271) employing the proposed dosing regimen and comparing the efficacy, safety, and tolerability of adalimumab vs. placebo and vs. methotrexate, but no PK data was obtained.

Pharmacokinetics:

In Study M02-528, the mean steady-state serum trough adalimumab levels during 40 mg EOW dosing for 12 weeks was 6.0 µg/mL (at Week 11, Regimen A) and was 17.6 to 18.2 µg/mL during 40 mg weekly dosing for 12 weeks (at Week 11 and 12, Regimen B). For Study M03-656, the mean steady-state serum trough adalimumab level during 40 mg EOW dosing (up to 52 weeks) was 5.2 µg/mL (at Week 33).

The mean steady-state serum trough adalimumab levels (5.2-6.0 µg/mL) for the above two trials combined were within the range of those observed in patients with RA (5 µg/mL), AS (6 to 7 µg/mL), PsA (6 to 10 µg/mL), and CD (7.2 µg/mL) during treatment with SC adalimumab 40 mg EOW as monotherapy. The population PK (PPK) analysis results showed that the median apparent clearance (CL/F: 21 mL/h) and apparent volume of distribution (Vd/F: 11.3 L) of adalimumab in the CPP patient population were similar to those obtained in other patient populations.

Basis for Dosing Regimen Selection:

In Study M02-528, at the end of 12 weeks of treatment, 53% of patients receiving Regimen A (a maintenance dose of 40 mg EOW) and 80% of patients receiving Regimen B (a maintenance dose of 40 mg weekly) achieved PASI75 (75% reduction in psoriasis area and severity index compared to baseline) or better compared to 4% of patients

receiving placebo. Regimen A reached 67% and regimen B reached 77% at a followed-up assessment at Week 24 (an extension study). The difference at Week 24 was not statistically significant and, therefore, the sponsor selected Regimen A for further clinical development.

Immunogenicity:

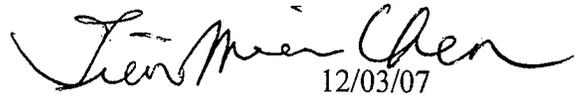
Overall Incidence rate: With Study M02-528 and M03-656 combined, the overall rate of anti-adalimumab antibody (AAA) formation in patients with psoriasis (8.4%; 77/920) appears to be in the range of those observed in patients with RA (12%; 54/434), AS (8.6%; 16/185), and PsA (13.5%; 24/178) during adalimumab 40 mg EOW monotherapy. However, the rate was higher than that (2.6%; 7/269) observed in patients with CD.

Incidence rate in CPP patients with psoriatic arthritis (PsA): Additional analyses were conducted by this reviewer. In Study M03-656, the percentage of CPP patients who had medical history of PsA and developed AAA+ was 3.0% (7/230), while the rate was 3.9% (23/597) for CPP patients who did not have medical history of PsA but developed AAA+. Therefore, there was no evidence that CPP patients who had medical history of PsA had a higher rate of immunogenicity for AAA+ development. In Study M02-528, the number of patients with PsA was too small to draw any conclusions.

Immunogenicity vs. adalimumab PK: For psoriasis, the development of AAA tended to be associated with reduced adalimumab exposure which was consistent with what was observed in other indications. Previous analyses for other indications had shown a similar trend of higher apparent clearance in patients with positive AAA development.

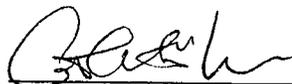
Immunogenicity vs. efficacy: The results obtained from Study M03-656 showed that patients who achieved a PASI75 response at Week 16 had mean steady-state serum adalimumab level (6.28 µg/mL) almost three fold higher than those in patients who did not achieve PASI75 response (2.24 µg/mL). Further analysis showed that 1) AAA+ patients had a statistically significantly lower PASI75 response rate than AAA- patients at Week 16 (11% vs. 76%; $p < 0.001$) and 2) the 'event' (i.e., loss of adequate response, i.e., PASI75) rate was significantly higher in AAA+ patients than that in AAA- patients (18% vs. 4%; $p=0.034$) at Week 52. Similar results were also obtained from Study M02-528 and all 3 out of 45 patients (Regimen A) tested with AAA+ had low or undetectable serum adalimumab levels starting Week 8 and none of those AAA+ patients achieved a PASI75 response.

Immunogenicity vs. safety: Regarding safety, there was no clear indication that the development of AAA increased safety risk in adalimumab-treated CPP patients.


12/03/07

Tien-Mien Chen, Ph.D.

Team Leader: Sue-Chih Lee, Ph.D.



12/03/07

2. Question Based Review

2.1 General Attributes

Mechanism of Action:

Psoriasis is a chronic immunologic disease characterized by marked inflammation and thickening of the epidermis that result in thick, scaly plaques involving the skin. It affects 1 to 3% of the general population. Plaque psoriasis is the most common type, constituting 75-80% of patients with psoriasis. Fingernail and joint involvement are sometimes associated, and up to 10% of patients may have associated PsA.

TNF (tumor necrosis factor), a naturally occurring pro-inflammatory cytokine, is an important contributor in the pathogenesis of psoriasis; elevated TNF levels have been found to play an important role in pathologic inflammation. TNF antibodies are a class of drugs that inhibit the pro-inflammatory cytokine TNF. Preliminary evidence of the therapeutic benefit of anti-TNF therapy in psoriasis has been shown with other agents.

Adalimumab is a recombinant human immunoglobulin (IgG₁) monoclonal antibody containing only human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system. It consists of 1,330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is comprised of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences.

Adalimumab binds to TNF- α (but not lymphotoxin, TNF- β) and neutralizes the biological function of human TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. It also modulates biological responses that are induced or regulated by TNF.

2.2 General Clinical Pharmacology

Q1. What are the design features of the clinical pharmacology and clinical studies used to support the application?

One Phase-2 trial (Study M02-528) and 2 Phase-3 trials (M03-656 and M04-716) formed the basis for evaluating adalimumab for the treatment of moderate to severe CPP. Blood samples were obtained for the evaluation of serum adalimumab levels and serum AAA from Study M-02-528 and M03-656.

A PPK approach was also employed for analyses of CL/F and Vd/F of adalimumab in this target patient population. A total of 827 patients were included in the NONMEM analysis (n = 733 from Study M03-656 and n = 94 from Study M02-528). Age, weight, sex, race (White: yes/no), body mass index (BMI), body surface area (BSA), history of PsA (yes/no), Baseline PASI score, AAA (yes/no) and study were identified as the covariates to be tested in the PK model building process.

The main clinical pharmacology studies, Studies M02-528 and M03-656 plus Study M04-716, are shown below in Table 1:

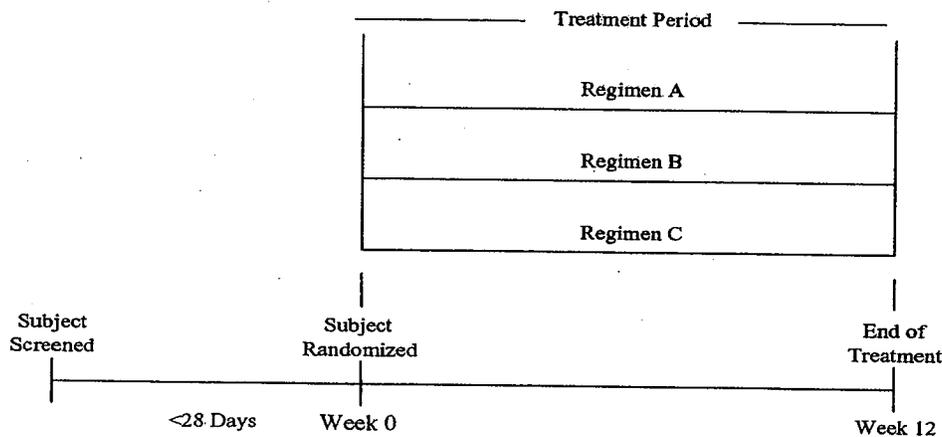
Table 1. Main Studies submitted under BLA125057/110 for Moderate to Severe Chronic Plaque Psoriasis

Study No. Duration	No. Patients Enrolled	Location/ Number of Sites	Study Design	Primary Objective	Status
Pivotal Studies					
M02-528 12 weeks	148 ^a	United States, Canada/ 18	Randomized, double-blind, placebo-controlled, multicenter, dose-ranging study in subjects with moderate to severe plaque psoriasis (BSA \geq 5%) and inadequate response to topical therapy Subjects were randomly assigned (1:1:1) to one of three treatment groups (adalimumab 40 mg eow, adalimumab 40 mg weekly, placebo)	Demonstrate adalimumab as an effective and safe therapy in subjects with moderate to severe chronic plaque psoriasis and to determine the optimal dose for clinical response	Study completed Eligible subjects may have rolled over into extension Study M02-529, and then into Study M03-658
M03-656 Period A: 16 weeks Period B: 17 weeks Period C: 19 weeks	Period A: 1212 Period B: 606 Period C: 490	United States, Canada/ 81	<u>Period A:</u> double-blind, placebo-controlled treatment period in subjects with moderate to severe chronic plaque psoriasis (PASI \geq 12, BSA \geq 10%); subjects were randomly assigned (2:1) to receive adalimumab 40 mg eow or placebo <u>Period B:</u> open-label treatment period; all subjects who achieved a \geq PASI75 response at Week 16 received adalimumab 40 mg eow <u>Period C:</u> double-blind, placebo-controlled treatment period; subjects who maintained a \geq PASI75 response at Week 33 and were originally randomized to active therapy in Period A were rerandomized (1:1) to receive adalimumab or placebo	<u>Period A:</u> confirm the short-term clinical efficacy, safety, and tolerability of adalimumab <u>Period B:</u> assess long-term efficacy, safety, and tolerability of adalimumab through 33 weeks of therapy <u>Period C:</u> compare continued adalimumab 40 mg eow therapy with withdrawal from active treatment (placebo) in subjects losing adequate response (i.e., achieving an event) after Week 33, and on or before Week 33	Study completed Eligible subjects may have rolled over into Study M03-658
M04-716 16 weeks	271	Europe, Canada/ 28	Randomized, double-blind, double-dummy, multicenter, placebo- and active-controlled study in subjects with moderate to severe plaque psoriasis (PASI \geq 10, BSA \geq 10%) who were candidates for systemic therapy or phototherapy and had inadequate response to topical therapy Subjects were randomly assigned (2:2:1) to one of three treatment groups (adalimumab 40 mg eow, MTX [7.5-25.0 mg], or placebo)	Compare the efficacy, safety, and tolerability of adalimumab vs. placebo and vs. MTX	Study completed Eligible subjects may have rolled over into Study M03-658

Study M02-528 was a 12-week, randomized, double blind, placebo-controlled, multicenter, Phase-2 efficacy and safety study. Patients were randomly assigned to one of three groups (two active treatment groups or placebo). Both active treatment arms received 80 mg adalimumab at baseline (Week 0). Patients assigned to the first arm (Regimen A) then received 40 mg every other week (EOW) starting with Week 1. Patients assigned to the second arm (Regimen B) then received another 80 mg at Week 1 followed by 40 mg adalimumab weekly starting with Week 2. The third arm (Regimen C) received placebo only, administered weekly, starting at baseline. To maintain the blind, all patients received a total of 2 injections at baseline and Week 1.

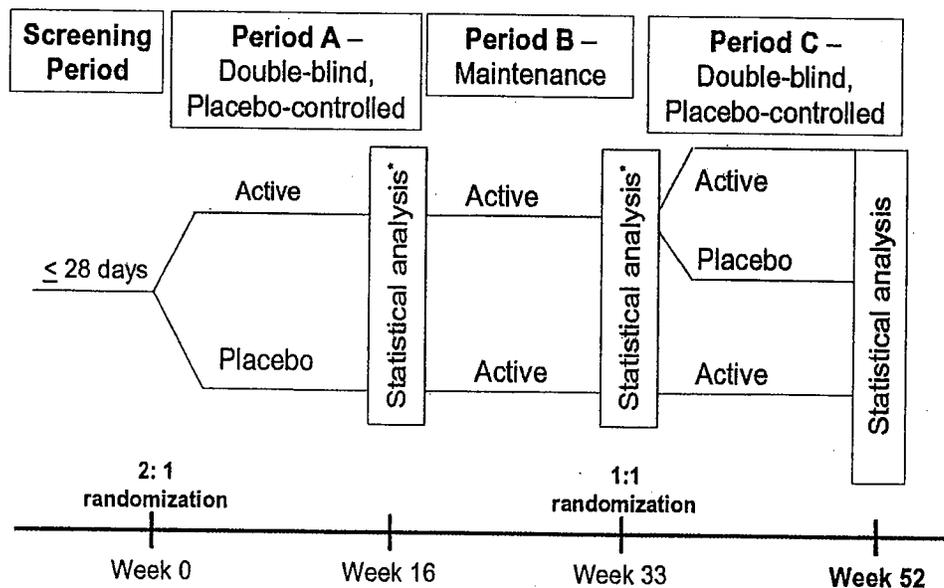
The study design was shown below in Scheme 1. Patients who completed 12 weeks of active treatment in Study M02-528 were given the opportunity to roll over into an extension study, M02-529. Blood samples were obtained for the evaluation of serum adalimumab levels (baseline and Weeks 1, 2, 4, 8, 11, and 12 or at early termination) and serum AAA levels (at baseline and Weeks 4, 8, 11, and 12 or at early termination).

StudyM02-528: Study Design (Scheme 1)



Study M03-656 was a short- and long-term, multi-center, Phase-3 efficacy and safety study. This study consisted of three treatment periods, Period A (16 weeks; N=1212), Period B (17 weeks; N=606), and Period C (19 weeks; N=490) as shown below in Scheme 2.

StudyM03-656: Study Design (Scheme 2)



* PASI 75 responders or better continue in the study

An initial dose of 80 mg adalimumab at baseline (Week 0) and then 40 mg EOW starting with Week 1 were employed to active arm of Period A. Period B assessed the safety and efficacy of adalimumab through 33 weeks of continuous therapy for those who had achieved PASI75 response at Week 16. Period C evaluated whether patients who had responded to adalimumab treatment during Periods A and B (33 weeks) lost their response when they underwent protocol-mandated discontinuation of adalimumab after Week 33 until Week 52 compared with patients who continued treatment with adalimumab. Blood samples were obtained for the evaluation of serum adalimumab and serum AAA levels (both at baseline and Weeks 16, 33, and 52 or at early termination).

Study M04-716, a third placebo-controlled confirmatory Phase-3 trial in patients with psoriasis (N=271) employing the proposed dosing regimen and comparing the efficacy, safety, and tolerability of adalimumab vs. placebo and vs. methotrexate, but no PK data was obtained.

Other extension trials included Study M02-529 (from Study M02-528), Study M03-596 (from Study M02-538), and Study M03-658 (an open-label extension study for patients who participated in Studies M02-529, M02-538, M03-596, M03-656, and M04-716). These study results were also submitted to support efficacy and safety.

Note: Study M02-528 allowed the study of moderate to severe patients with BSA involvement of > 5%, whereas Studies M03-656 and M04-716 enrolled moderate to severe psoriasis patients restricted to Baseline BSA \geq 10%.

Exposure-Response Evaluation

Q2. How were the dose and dosing regimen selected?

The Phase 2 study, M02-528, investigated the clinical efficacy and safety of adalimumab vs. placebo using two maintenance SC dose regimens for 12 weeks in the treatment of subjects with moderate to severe CPP. These patients were treated in the extension study for an additional 12 weeks. Efficacy variables used were 1). proportion of patients with a \geq PASI75 response rate (primary) and 2). patients with a Physician's Global Assessment (PGA) severity score of clear or minimal.

At the end of 12 weeks of treatment, 53% of patients receiving Regimen A (a maintenance dose of 40 mg EOW) and 80% of patients receiving Regimen B (a maintenance dose of 40 mg weekly) achieved PASI75 or better compared to 4% receiving placebo. However, the response rates of the two different dosage groups converged considerably when these two groups were followed up for an additional 12 weeks in the extension study. Regimen A reached 67% and regimen B reached 77% at a followed-up assessment at Week 24 (an extension study). The difference was small and not statistically significant. Therefore, Regimen A was selected for further clinical development.

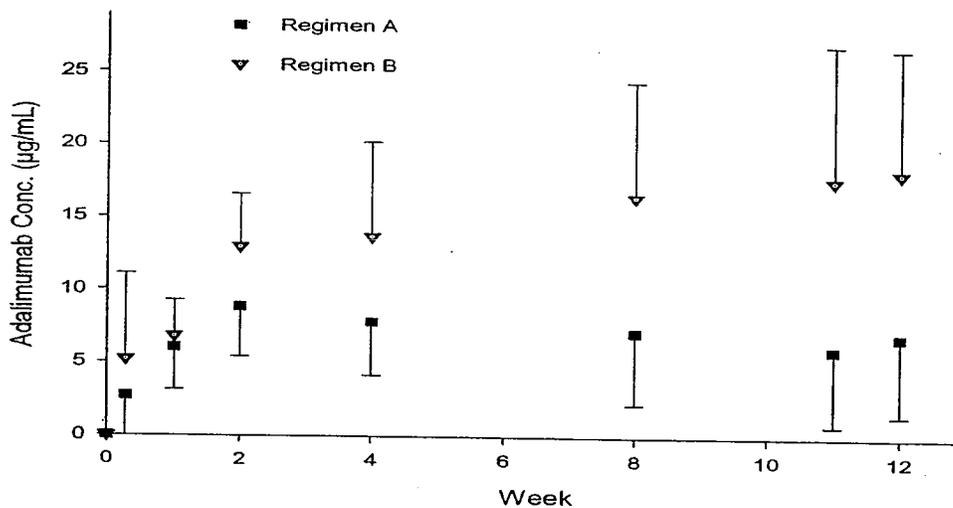
Pharmacokinetic Characteristics

Q3: What are the PK characteristics in patients with CPP after SC Injection?

The overall mean steady-state trough adalimumab level in patients with CPP was 5.2 to 6.0 µg/mL during the 40 mg EOW dosing (Study M02-528 and M03-656 combined). It was within the range of those observed in patients with RA (5 µg/mL), AS (6 to 7 µg/mL), and PsA (6 to 10 µg/mL) during treatment with SC adalimumab 40 mg EOW as monotherapy. The PPK results showed that the median CL/F (21 mL/h) and Vd/F (11.3 L) of adalimumab in the CPP patient population were similar to those obtained in other patient populations.

For Study M02-528, the mean steady-state serum trough adalimumab levels during 40 mg EOW dosing up to 12 weeks was 6.0 µg/mL (at Week 11, Regimen A) and were 17.6 and 18.2 µg/mL during 40 mg weekly dosing (at Weeks 11 & 12, Regimen B) as shown in Figure 1.

Figure 1. Summary of Mean (\pm SD) Serum Trough Adalimumab Profiles obtained from Study M02-528



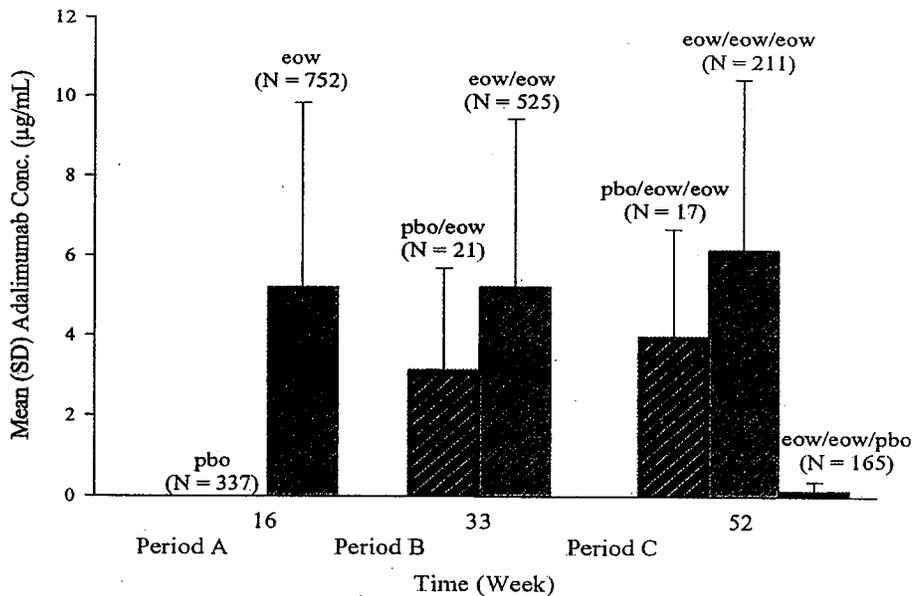
For Study M03-656, mean steady-state serum adalimumab levels at weeks 16, 33 and 52 were 5.20 to 6.15 µg/mL during the 40 mg EOW continuously active dosing for 52 weeks (EOW/EOW/EOW; Table 2 and Figure 2). Note that only the mean steady-state serum adalimumab level at Week 33 (5.22 µg/mL) was trough level.

Table 2. Mean Serum Adalimumab Concentrations obtained at the End of Each Study Period (16, 33, or 52 Weeks)

Week 16 (End of Period A and Start of Period of B)			
	<u>Pbo</u> Placebo (N= 355)	<u>EOW</u> Adalimumab (N= 783)	
N	337	752	
Mean	0.00	5.20	
SD (CV%)	0.00 (----)	4.64 (89%)	
Week 33 (End of Period B and Start of Period of C), Trough Levels*			
	<u>Pbo/EOW</u> Adalimumab (N= 23)	<u>EOW/EOW</u> Adalimumab (N= 550)	
N	21	525	
Mean	3.14	5.22	
SD (CV%)	2.55 (81%)	4.23 (81%)	
Week 52 (End of Period C)			
	<u>Pbo/EOW/EOW</u> Adalimumab (N= 18)	<u>EOW/EOW/Pbo</u> Placebo (N= 184)	<u>EOW/EOW/EOW</u> Adalimumab (N= 227)
N	17	165	211
Mean	3.99	0.142	6.15
SD (CV%)	2.69 (67%)	0.229 (161%)	4.29 (70%)

*. Steady-state adalimumab levels at Week 33 only were trough levels.

Figure 2. Summary of Mean (\pm SD) Serum Adalimumab Levels obtained from Study M03-656



PPK analysis: A total of 827 psoriasis patients were included in the NONMEM analysis (n=733 from Study M03-656 and n=94 from Study M02-528) using a one-compartment model. Summary statistics for the post-hoc estimates of CL/F and V/F for Study M02-528 and M03-656 combined are provided in Table 3 below. The median CL/F of adalimumab was 21 mL/hr. It is similar to that observed in patients with RA treated with adalimumab 40 mg EOW as monotherapy (24 mL/h). Clearance tended to increase with increasing body weight. The median V/F of adalimumab was 11.3 L in patients with psoriasis, which is comparable to that observed in RA (11.2 L).

Table 3. Summary Statistics for CL/F and V/F of Adalimumab in Patients with Psoriasis

Parameter	N	Mean	std	CV	Geo_m	Min	P5	Q1	Median	Q3	P95	Max
CLF(mL/h)	827	25.93	16.14	62.2	21.60	4.19	8.13	13.90	20.78	34.48	58.85	103.47
V/F(L)	827	11.45	2.27	19.8	11.23	3.19	8.26	10.14	11.27	12.50	15.39	24.20

Geo_m = geometric mean.

P5, Q1, Q3 and P95 = 5th, 25th, 75th and 95th percentiles, respectively.

Q4: What is the incidence rate of AAA development in the CPP patient population and how does it compare with other patient populations?

With Study M02-528 and M03-656 combined, the overall rate of AAA formation (8.4%; 77/920) in patients with CPP appears to be in the range of those observed in patients with RA (12%; 54/434), AS (8.6%; 16/185), and PsA (13.5%; 24/178) during adalimumab 40 mg EOW monotherapy. However, they were all higher than that (2.6%; 7/269) observed in patients with CD.

In Study M03-656, 825 patients received at least one dose of adalimumab and had at least one blood sample for AAA level taken after the first adalimumab dose. There were 73 out of 825 patients (8.8%) tested AAA+ at least once during the study period.

In Study M02-528, the immunogenicity of AAA was found in 3 out of 45 (6.7%) patients (Regimen A) and 1 out of 50 (2%) patients (Regimen B). Note that the sample size was small in this study.

Q5: Did patients who had lower serum adalimumab levels have a lower response rate, i.e., reaching PASI75?

Yes, there was indication that patients with lower serum adalimumab concentrations were less likely to respond to the treatment.

In Study M03-656, patients who achieved PASI75 response at Week 16 had a mean steady-state serum adalimumab level of 6.28 µg/mL, almost three fold higher than those in patients who did not achieve PASI75 response (2.24 µg/mL; see Table 4 below).

Table 4. Summary Statistics of Adalimumab Serum Levels (µg/mL) for Adalimumab Treatment Group at Week 16 Stratified by PASI75 Response (M03-656)

Study M03-656	PASI75 Response	
	No (N=208)	Yes (N=575)
N	201	551
Mean (µg/mL)	2.24	6.28
SD (CV%)	3.22 (144%)	4.61 (73%)
Range	0.00 – 14.4	0.00 – 47.5

Q 6. Did immunogenicity have impact on efficacy?

For psoriasis, the development of AAA was associated with reduced efficacy. This is consistent with what was observed in other indications.

In Study M03-656, AAA+ patients had a statistically significantly lower PASI75 response rate than AAA- patients at Week 16 (11% vs. 76%; p < 0.001) as shown in Table 5 below.

Table 5. Summary of PASI75 Response at Week16 (Double-Blind Period A)

Analysis			PASI75 Response			
Non-Responder Imputation	Subgroup	N	Responder n (%)	Non Responder n (%)	Missing	p-value
	AAA+	45	5 (11.1%)	39 (86.7%)	1 (2.2%)	<0.001
	AAA-	742	562 (75.7%)	153 (20.6%)	27 (3.6%)	

Furthermore in the double-blind Period C of Study M03-656, the results obtained from the patients enrolled in EOW/EOW/EOW treatment group showed that the 'event' (i.e., loss of adequate response, PASI75) rate was significantly higher in AAA+ patients than that in AAA- patients (18% vs. 4%; p=0.034, Table 6). [Note: For the EOW/EOW/Pbo group, the 'event' rate was lower in AAA- patients, however, the difference between AAA+ and AAA- patients was not significant (43 % vs. 28%; p = 0.388), which was not surprising as all the patients were on placebo (Table 6).]

Table 6. Proportion of Patients Experiencing an 'Event' (i.e., Loss of Adequate Response) after Week 33 and on or before Week 52 (Non-Responder Imputation, Double-Blind Period C)

Analysis			PASI75 Response	
Treatment	Subgroup	N	Loss of Adequate Response	p-value
EOW/EOW/EOW	AAA+	11	2 (18.2%)	0.034
	AAA-	239	10 (4.2%)	
EOW/EOW/Pbo	AAA+	7	3 (42.9%)	0.388
	AAA-	233	65 (27.9%)	

In Study M02-528, all four patients tested with AAA+ had much lower (or undetectable) serum adalimumab levels starting Week 8 and none of the four AAA+ patients achieved a PASI75 response, whereas 57% and 82% of AAA- patients were PASI75 responders in the 40 mg EOW group (Regimen A) and in the 40 mg weekly group (Regimen B), respectively. Again, the sample size in this study is small for any definitive conclusion.

Q7. Did immunogenicity have impact on adalimumab PK?

Previous studies for other indications revealed that there was a trend towards lower serum adalimumab concentrations in patients who developed AAA. For the current indication, it is noted that, in study M02-528, all four patients (3 with Regimen A and one with Regimen B) who were AAA+ had very low serum adalimumab concentrations (Tables 7 and 8).

Table 7. Mean Serum Adalimumab Levels (µg/mL), Study M02-528

Regimen A (n=45), Study M02-528					
Sampling Time	No Medical History of Psoriatic Arthritis		With Medical History of Psoriatic Arthritis		
	N	Mean Conc. (µg/mL)	N	Total	*AAA + (n=3)
				Mean Conc. (µg/mL)	Mean Conc. (µg/mL)
Baseline	29	0.00	15	0.00	
Week 1	27	6.03	15	6.05	
Week 2	25	9.37	15	7.96	
Week 4	28	8.18	15	7.11	
Week 8	28	8.31	15	4.92	0.66
Week 11	27	7.38	15	3.52	BLQ
Week 12	27	8.16	15	4.64	BLQ

*. Patients with AAA +: #s. 525, 2012, and 2430 (n=3)

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Table 8. Mean Trough Serum Adalimumab Levels (µg/mL), Study M02-528

Regimen B (n=50), Study M02-528					
Sampling Time	No Medical History of Psoriatic Arthritis		With Medical History of Psoriatic Arthritis		
	N	Mean Conc. (µg/mL)	N	Total	*AAA + (n=1)
				Mean Conc. (µg/mL)	Mean Conc. (µg/mL)
Baseline	37	0.00	12	0.00	
Week 1	36	6.84	10	6.61	
Week 2	35	13.0	11	12.6	
Week 4	38	13.0	11	13.1	
Week 8	37	16.1	10	17.8	0.46
Week 11	33	17.1	10	19.4	BLQ
Week 12	36	17.9	10	19.2	BLQ

*. Patient with AAA +: # 327 (n=1)

Q8. Did AAA development impact the safety of adalimumab?

In Study M03-656, there was no clear indication that the development of AAA increased safety risk in adalimumab-treated CPP patients (Table 9) although the incidence rate for serious AE was somewhat higher for the AAA+ patients.

Table 9. Overview of No. and % with Treatment-Emergent Adverse Events (Study M03-656)

	AAA+	AAA-
	(N = 73)	(N = 750)
	n (%)	n (%)
Subjects with:		
Any AE	46 (63.0)	588 (78.4)
Any AE at least possibly drug-related ^s	14 (19.2)	217 (28.9)
Any severe AE	3 (4.1)	38 (5.1)
Any serious AE	3 (4.1)	25 (3.3)
Any AE leading to discontinuation of study drug	2 (2.7)	27 (3.6)
Any fatal AE	0	0
Infections	20 (27.4)	362 (48.3)
Serious infections	0	10 (1.3)
Malignancies	0	8 (1.1)
Lymphoma	0	0
Non-melanoma skin cancers	0	6 (0.8)
Other malignancies	0	2 (0.3)
Demyelinating disorders	0	0
Congestive heart failure	0	1 (0.1)
Injection site reaction	1 (1.4)	68 (9.1)

Q9: Did CPP patients who had medical history of PsA have higher rate of immunogenicity for AAA+ development?

There was no evidence that CPP patients with a medical history of PsA had a higher rate of immunogenicity.

The following analyses were conducted by this reviewer. Based on Study M03-656, CPP patients with or without medical history of PsA appeared to have a comparable rate of immunogenicity for AAA+ development. There were 3.0% (7/230) of patients with medical history of PsA and 3.9% (23/597) of patients without medical history of PsA who developed AAA+ (Table 10).

Table 10. Study M03-656

	Patients With Medical History of Psoriatic Arthritis	Patients Without Medical History of Psoriatic Arthritis
AAA+	7/230 (3.0%)	23/597 (3.9%)
AAA -	223/230 (97%)	574/597 (96.1%)

Results obtained from Regimen A of Study M02-528 showed a greater incidence rate in immunogenicity for patients with a history of PsA (Table 11). However, the sample size in this study was much smaller than that in Study M03-656.

Table 11. Study M02-528 (Regimen A)

	With Medical History of Psoriatic Arthritis	Without Medical History of Psoriatic Arthritis
AAA+	3/15 (20%)	0/29 (0%)
AAA -	12/15 (80%)	29/29 (100%)

2.3 Intrinsic Factors:

No intrinsic factors have been identified as clinically significant that warrant dosage adjustment.

In the approved label, gender was not identified as a significant factor influencing the adalimumab PK when body weight was taken into consideration.

In the current PPK analysis, body weight was a statistically significant factor for the adalimumab PK. Because of this, the sponsor evaluated the potential effect of weight on PASI score at Week 16 using the data from two pivotal studies, Study M03-656 Period A

(a 16-week period) and M04-716 (a 16-week study). The results show that the percentage of PASI75 responders in the fourth weight quartile was 15% less than that in the first weight quartile (62% vs. 77%), even though the weight increased about three fold from the first to the fourth weight quartile. In addition, weight, as a univariate predictor, accounted for less than 2% of the overall variability in adalimumab efficacy. Therefore, weight-adjusted dosing of adalimumab in adult psoriatic patients was not considered necessary.

2.4 Extrinsic Factors:

Immunogenicity has been discussed above.

2.5 General Biopharmaceutics:

The to-be-marketed formulation (i.e., the currently approved formulation) of Humira, single-use 1-mL prefilled glass syringes (40 mg/0.8 mL) and vials were employed in the studies. Therefore, no comparability studies are necessary.

2.6 Analytical Section

Q10: Are the analytical methods employed for determinations of serum adalimumab and AAA levels and their validation reports acceptable?

Serum samples were analyzed for adalimumab concentrations using a validated double antigen immunoassay ELISA assay. The analytical assays and validation reports were not optimal, but acceptable.

For Study M02-528, an was used for determining serum adalimumab concentrations. b(4)

For study M03-656, serum samples were analyzed for adalimumab concentrations at Abbott GmbH & Co KG, GPRD, Knollstrasse 50, D-67061, Ludwigshafen, Germany.

Adalimumab Assay:

For the evaluation of serum adalimumab concentrations, blood samples were obtained at baseline and Weeks 1, 2, 4, 8, 11 and 12/Early Termination and the Follow-up visit, if appropriate (Study M02-528) and at baseline, Week 16, Week 33, and Week 52 or the appropriate Early Termination (A, B, or C) visit (Study M03-656). Blood sample was allowed to clot for 30 min at room temperature prior to centrifugation.

For Study M02-528, samples were analyzed for serum adalimumab levels using an ELISA method (a double antigen immunoassay) at under the supervision of Abbott Lab. The assay range was from 2.50 to 50.0 ng/mL in diluted serum. The limit of quantitation (LOQ) was reported to be 2.50 ng/mL in diluted b(4)

serum (equivalent to 250.0 ng/mL in undiluted serum) for adalimumab. In-study quality control (QC) samples (5.40, 11.9, 18.7, and 29.8 ng/mL) demonstrated a coefficient of variation (CV) values of $\leq 6.80\%$ (precision) and the mean analytical recoveries ranged between 95.0% and 101.3 % (accuracy) of their theoretical values.

For Study M03-656, samples were analyzed for serum adalimumab levels using a validated ELISA method (a double antigen immunoassay) at Abbott GmbH & Co. (Ludwigshafen, Germany). The assay range was from 3.13 to 50.0 ng/mL in diluted serum. The limit of quantitation (LOQ) was reported to be 3.13 ng/mL in diluted serum (equivalent to 31.3 ng/mL in undiluted serum) for adalimumab. In-study quality control (QC) samples (10.0, 20.0, and 40.0 ng/mL) demonstrated a coefficient of variation (CV) values of $\leq 11.6\%$ (precision) and the mean analytical recoveries ranged between 97.2% and 98.6% (accuracy) of their theoretical values.

AAA Assay:

For the evaluation of serum AAA levels, blood samples were obtained at baseline and Weeks 4, 8, 11, 12/Early Termination and the Follow-up visit, if appropriate (Study M02-528) and at baseline, Week 16, Week 33, and Week 52 or the appropriate Early Termination (A, B, or C) visit (Study M03-656).

Since serum adalimumab level interferes with the ELISA for serum AAA level determination, only those samples where serum adalimumab levels were $< 2 \mu\text{g/mL}$ upon sample collection were chosen and analyzed for serum AAA levels.

Serum samples were analyzed for AAA using a validated double antigen immunoassay ELISA assay at Abbott GmbH & Co KG, GPRD, Knollstrasse 50, D-67061, Ludwigshafen, Germany. The assay detects antibodies directed against epitopes on the entire adalimumab molecule. The assay range was from 0.50 to 5.0 ng/mL in diluted serum. The LOQ for AAA was established at 0.5 ng/mL in diluted serum or 5 ng/mL in undiluted serum. In-study QC samples, supplemented with concentrations of 0.75, 1.5, 2.5, 3.5, and 4.75 ng/mL of \square anti-adalimumab antibodies, were analyzed with the unknowns. The % CV values were $\leq 5.31\%$ (precision) and the mean analytical recoveries ranged between 91.9% and 100.9% (accuracy) of their theoretical values.

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3. Detailed Labeling Recommendations

Labeling Comment: Sponsor proposed addition (black and underline) and Agency proposed addition (blue and double underline):

Under subsection 12.3 Pharmacokinetics of Section 12. Clinical Pharmacology, the 7th paragraph should be revised as follows:

In patients with psoriasis, the mean steady-state trough concentration was approximately 5 to 6 $\mu\text{g/mL}$ during adalimumab 40 mg every other week monotherapy treatment.

4. Appendices

- 4.1 Proposed Package Insert (Original and Annotated)
- 4.2 Individual Study Review
- 4.3 Cover Sheet and OCPB Filing/Review Form

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BLA125057/89 for Humira SC Injectable Solution

Appendix 4.1

**Sponsor's Proposed Labeling
(March, 2007 Version)**

42 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

BLA125057/89 for Humira SC Injectable Solution

Appendix 4.2

Synopses of Individual Studies



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Adalimumab (D2E7, LU 200134)		
Name of Active Ingredient: Adalimumab		
Title of Study: Pharmacokinetic Assessments from a Phase 2 Trial Titled "A Phase II Multicenter Study of the Safety and Efficacy of Adalimumab (D2E7) in Subjects with Moderate to Severe Chronic Plaque Psoriasis"		
Study Sites: 18 sites in the United States and Canada		
Publications: Not applicable.		
Studied Period: Approximately 12 Weeks Study Initiation Date: 11 March 2003 (first subject screened) Study Completion Date: 25 September 2003 (last subject completed)		Phase of Development: 2
Objective: The objective of this study was to investigate the clinical efficacy and safety of subcutaneously administered adalimumab vs. placebo using two dose regimens for 12 weeks in the treatment of subjects with moderate to severe chronic plaque psoriasis. This report focuses on the pharmacokinetic assessments performed in this study.		
Methodology: This was a 12-week, randomized, double blind, placebo-controlled, multicenter, efficacy and safety study designed to demonstrate the effectiveness of adalimumab in the treatment of subjects with moderate to severe psoriasis. Subjects were randomly assigned to one of three groups (two active treatment groups or placebo). Both active treatment arms received 80 mg adalimumab at Baseline (Week 0). Subjects assigned to the first arm (Regimen A) then received 40 mg every other week (eow) starting with Week 1. Subjects assigned to the second arm (Regimen B) then received 80 mg at Week 1 followed by 40 mg adalimumab weekly starting with Week 2. The third arm (Regimen C) received placebo only, administered weekly, starting at Baseline. In order to maintain the blind, all subjects received a total of 2 injections at Baseline and Week 1. During the remaining treatment period (Weeks 2 through 12), subjects received one injection per week. The treatment dose per injection corresponded to the dose regimen randomly assigned to each subject. Efficacy and safety measurements were performed throughout the study. Blood samples were obtained at Baseline and Weeks 1, 2, 4, 8, 11 and 12/Early Termination and the Follow-up visit, if appropriate, for the evaluation of serum adalimumab concentration. Blood samples were also obtained at Baseline and Weeks 4, 8, 11, 12/Early Termination and the Follow-up visit, if appropriate, for the evaluation of serum anti-adalimumab antibodies (AAA).		

Number of Subjects (Planned and Analyzed):

Planned: 150; Randomized: 148; Dosed: 147; Completed: 140; Evaluated for Pharmacokinetics: 95
A total of 95 subjects received Treatment A or Treatment B and were included in the pharmacokinetic analyses. These subjects ranged in age from 20 to 86 years, with an average age of 44.7 years. Most subjects (60 of 95 [68.4%]) were male and the majority (85 of 95 [89.5%]) was white. The mean weight and height was 95.6 kg (range: 42 to 160 kg) and 173.0 cm (range: 149 to 196 cm), respectively. Subjects with a medical history of psoriatic arthritis represented 28.4% (27 of 95) of subjects included in the pharmacokinetic analyses.

For the 94 subjects (64 males and 30 females) who were included in the population pharmacokinetic analyses (one subject, 210, had no detectable concentration levels and was therefore not included), the mean age was 44.8 years (ranging from 20 to 86 years), the mean weight was 95.8 kg (ranging from 42 to 160 kg), the mean BSA was 2.08 m² (ranging from 1.38 to 2.69 m²) and 27.7% (26 of 94) were subjects with a medical history of psoriatic arthritis.

Subject Characteristics: Subjects were male and female volunteers age 18 years and older who had a clinical diagnosis of moderate to severe chronic plaque psoriasis defined by $\geq 5\%$ Body Surface Area (BSA) involvement for at least 1 year, active psoriasis, despite topical therapies, defined by $\geq 5\%$ BSA involvement at screening and baseline and were able to self-inject study medication or have a designee or nurse who could inject the study medication. Females, of childbearing potential, were not pregnant and were practicing an acceptable method of birth control.

Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:

	Placebo	Adalimumab
Dosage Form	Injectable Solution	Injectable Solution
Strength	0 mg in 0.8 mL	40 mg in 0.8 mL
Concentration	0 mg/mL	50 mg/mL
Mode of Administration	Subcutaneous	Subcutaneous
Formulation Lot	Abbott 90-014HK	Abbott 129005

Duration of Treatment: Approximately 12 weeks.

Criteria for Evaluation:

Pharmacokinetic: In addition to characterizing adalimumab serum concentration at each time of scheduled sampling, pharmacokinetic model based analyses was performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F).

Statistical Methods:

Pharmacokinetic: Adalimumab concentration data were summarized by treatment group at each time point using descriptive statistics including number of subjects (N), number of non-missing observations (n_{miss}), mean, median, standard deviation (SD), coefficient of variation, minimum, and maximum. Individual subject concentration vs. time plots, and mean concentration vs. time plots by treatment group are provided.

Population Pharmacokinetic: Population pharmacokinetic models were built using a non-linear mixed-effect population modeling approach with the NONMEM software (double precision, Version V, Level 1.1) and NMTRAN pre-processor 1. Models were run using the Compaq Visual Fortran Compiler (Version 6.6) on a Dual Processor Workstation (DELL Precision 530) under the Windows 2000 (service pack 4) operating system.

Summary/Conclusions:

Pharmacokinetic Results: Descriptive statistics of serum adalimumab concentrations for the adalimumab treatment groups Regimen A (80 mg sc on Week 0, 40 mg sc eow starting at Week 1) and Regimen B (80 mg sc on Week 0 and Week 1, 40 mg sc weekly starting at Week 2) are presented in the following tables.

Descriptive Statistics of Serum Adalimumab Concentrations Following Treatment of Subjects with Psoriasis with Regimen A (80 mg Loading Dose on Week 0 Followed by 40 mg eow Starting with Week 1)

	Week						
	0	1	2	4	8	11	12
n_{miss}	44	42	40	43	43	42	42
Mean ($\mu\text{g/mL}$)	0.00	6.03	8.84	7.81	7.13	6.00	6.91
SD ($\mu\text{g/mL}$)	0.00	2.89	3.41	3.67	4.91	5.18	5.39
Min ($\mu\text{g/mL}$)	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Median ($\mu\text{g/mL}$)	0.00	6.05	8.75	7.30	6.70	5.30	6.70
Max ($\mu\text{g/mL}$)	0.00	11.50	16.20	17.60	17.40	18.80	20.00
CV (%)	--	48	39	47	69	86	78
Geometric Mean ($\mu\text{g/mL}$)	--	6.03	8.50	7.17	5.64	5.23	6.96

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Descriptive Statistics of Serum Adalimumab Concentrations Following Treatment of Subjects with Psoriasis with Regimen B (80 mg Loading Dose on Week 0 and 1 Followed by 40 mg Every Week Starting with Week 2)

	Week						
	0	1	2	4	8	11	12
n _{miss}	49	46	46	49	47	43	46
Mean (µg/mL)	0.00	6.79	12.92	13.65	16.44	17.62	18.16
SD (µg/mL)	0.00	2.50	3.68	6.51	7.91	9.31	8.51
Min (µg/mL)	0.00	0.00	7.00	0.00	0.46	0.00	0.00
Median (µg/mL)	0.00	6.50	12.45	14.00	15.80	16.20	17.30
Max (µg/mL)	0.00	12.80	22.40	30.60	34.40	39.60	38.00
CV (%)	--	37	29	48	48	53	47
Geometric Mean (µg/mL)	--	6.56	12.42	12.78	13.71	14.85	16.49

Steady-state serum concentrations of adalimumab in subjects with psoriasis on the 40 mg weekly maintenance regimen (Regimen B) were a little more than double the steady-state concentrations obtained in subjects with psoriasis on the every other week regimen (Regimen A). The mean steady-state serum adalimumab trough concentration measured at Week 11 for the 40 mg sc eow (Regimen A) and 40 mg sc weekly (Regimen B) regimens were 6.00 µg/mL and 17.6 µg/mL, respectively.

Anti-adalimumab antibodies (AAA) were found in 3 of 45 (6.7%) subjects with psoriasis in the adalimumab 40 mg eow group (Regimen A) and 1 of 50 (2%) subjects with psoriasis in the adalimumab 40 mg weekly group (Regimen B). The overall percentage of subjects with psoriasis with measurable AAA during 12 weeks of treatment with adalimumab was 4.2% (4 of 95 subjects).

Population Pharmacokinetic Results:

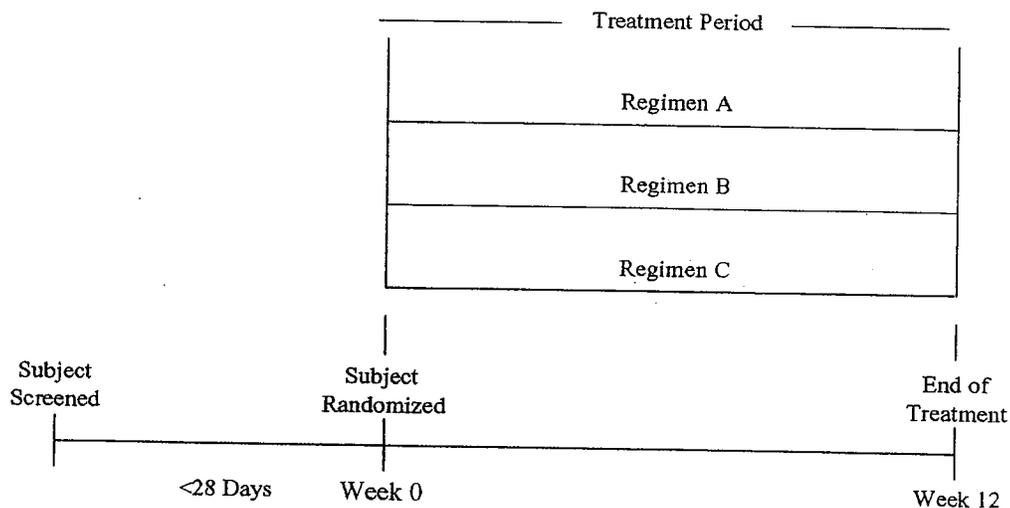
A one-compartment model with exponential inter-individual random effects on V/F and CL/F, and a combined residual error model was used as a base model for identification of covariates. Several covariates (BMI, BSA, PsA, sex and race) were tested by adding each covariate separately to the base model. A significant relationship between BSA and volume of distribution could be identified, whereas inclusion of other covariates did not further decrease the objective function in a significant manner.

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Conclusions: Steady-state serum adalimumab concentrations were achieved in subjects with psoriasis with Regimen A (80 mg at Week 0; 40 mg every other week starting with Week 1) within the first few weeks of treatment and were achieved more quickly with Regimen A than Regimen B (80 mg at Week 0 and Week 1; 40 mg weekly starting with Week 2). The mean serum adalimumab trough concentrations measured at Week 11 for Regimen A (80 mg at Week 0; 40 mg every other week starting with Week 1) and Regimen B (80 mg at Week 0 and Week 1; 40 mg weekly starting with Week 2) were 6.00 µg/mL and 17.6 µg/mL, respectively. The percentage of subjects positive for AAA during 12 weeks of treatment with adalimumab was 4.2%. This rate of AAA formation is similar to the 5.5% rate observed for subjects with rheumatoid arthritis.

From the population pharmacokinetic analysis, the median post-hoc clearance (CL/F) was estimated to be 13.45 mL/h for all subjects (n=94) with moderate to severe psoriasis and 15.75 mL/h (n=26) for subjects with a medical history of psoriatic arthritis. From cross-study comparisons, the clearance in subjects with moderate to severe psoriasis appears to be lower than the observed clearance in subjects with rheumatoid arthritis on adalimumab monotherapy. The median clearance in subjects with rheumatoid arthritis observed in Study DE011 with 40 mg weekly (40 mg biweekly) dosing was calculated to be 18.10 mL/h (23.93 mL/h). The analysis of covariate-parameter relationships revealed that the elimination of adalimumab is modestly dependent on body surface area.

StudyM02-528: Study Design (Scheme 1)



Regimen A	Adalimumab (D2E7) 80 mg sc was administered at Week 0 (baseline); D2E7 40 mg sc every other week was administered starting at Week 1 through Week 11, with placebo administered on alternate weeks.
Regimen B	Adalimumab (D2E7) 80 mg sc was administered starting at Week 0 (baseline) and at Week 1; D2E7 40 mg sc weekly was administered starting at Week 2 through Week 11.
Regimen C	Placebo sc was administered at baseline and then weekly through Week 11, with two injections given at Week 0 and Week 1.

Reviewer's Comments:

The study was reviewed and found acceptable. Please see the clinical pharmacology review text for details.

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2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Study Drug: Adalimumab, D2E7	Volume:	
Name of Active Ingredient: Adalimumab	Page:	
Title of Study: Pharmacokinetic Assessments from a Phase 3 Trial Titled: "A Phase 3, Multicenter Study of the Efficacy and Safety of Long-Term Adalimumab Treatment in Subjects with Moderate to Severe Chronic Plaque Psoriasis"		
Study Sites: Eighty-two (82) sites in the United States and Canada.		
Publications: Not applicable.		
Studied Period: 52 weeks		Phase of Development: 3
Study Initiation Date: 13 Dec 2004 (first subject screened) 21 Dec 2004 (first subject dosed)		
Last Subject Last Dose Date: 28 Jun 2006 (last subject last dosed)		
<p>Objectives:</p> <p>The objective of this study was to confirm the short- and long-term clinical efficacy and safety of subcutaneously administered adalimumab, as well as determine the proportion of subjects losing an adequate response (<i>i.e.</i>, experiencing an 'event') after Week 33 and on or before Week 52 after withdrawal of long-term continuous adalimumab therapy in the treatment of adult subjects with moderate to severe chronic plaque psoriasis.</p> <p>This report utilized the demographic, pharmacokinetic, immunogenicity and immunogenicity-related safety and efficacy data through Week 52 to assess the pharmacokinetics and immunogenicity of adalimumab. Detailed safety and efficacy data through Week 52 are reported separately.</p>		

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Methodology:

This was a short- and long-term, multi-center, efficacy and safety study using adalimumab in the treatment of subjects with moderate to severe plaque psoriasis. This study consisted three treatment periods:

- Period A: A 16-week, double-blind, placebo-controlled treatment period where subjects were randomized in a 2:1 ratio to receive adalimumab or placebo for an evaluation of efficacy and safety;
- Period B: A 17-week, open-label adalimumab treatment period for an evaluation of continued response in all subjects who achieved at least a Psoriasis Area and Severity Index (PASI) 75 response at Week 16 (the end of Period A) relative to Baseline (Week 0); and
- Period C: A 19-week, double-blind, placebo-controlled treatment period where subjects who maintained at least a PASI 75 response at Week 33 (the end of Period B), and were originally randomized to active therapy in Period A, were re-randomized in a 1:1 ratio to receive adalimumab or placebo to compare the proportion of subjects losing an adequate response (*i.e.*, experiencing an 'event') after Week 33 and on or before Week 52 in the two treatment groups.

Blood samples for serum adalimumab and anti-adalimumab antibody (AAA) assays were obtained at Baseline, Week 16, Week 33 and Week 52 visits or at Early Termination A, B or C visit. Both adalimumab and AAA were assayed by means of validated enzyme-linked immunosorbent assay (ELISA) methods based on a double-antigen technique.

Adalimumab and AAA samples were analyzed at Abbott.GmbH & Co. (Ludwigshafen, Germany). The limit of quantitation (LOQ) for adalimumab was established at 3.13 ng/mL in diluted serum or 31.25 ng/mL in undiluted serum. The LOQ for AAA was established at 0.5 ng/mL in diluted serum or 5 ng/mL in undiluted serum. To meet assay criteria, only samples in which the adalimumab concentration was low (< 2 µg/mL) were to be selected for AAA assay. Serum samples were considered to be positive for AAA (AAA+) if all of the following criteria were met: the measured AAA concentration was greater than 20 ng/mL; the signal was not reduced by 50% or more by addition of 10% human serum; and the serum sample was collected within 30 days after an adalimumab dose.

Number of Subjects (Planned and Analyzed):

Planned: 1200; Randomized: 1212 (398 into the placebo group and 814 into the adalimumab group in Period A); Completed (up to Week 52): 429.

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The following table summarizes the disposition of subjects in the study.

Total Number of Subjects (N = 1212)			
Period A			
	Placebo	Adalimumab	
Entered	398	814	
Completed	355	783	
Early terminated	43	31	
Period B			
	Adalimumab	Adalimumab	
Entered	26	580	
Completed	23	550	
Early terminated	3	30	
Period C			
	Adalimumab	Placebo	Adalimumab
Entered	22	240	250
Completed	18	184	227
Early terminated	4	56	23

The summary demographics for all subjects who entered the study and were randomized in Period A are shown in the following table.

All Subjects Randomized in Period A (N = 1212)		
Mean ± SD (Range)		
Age (years)	44.5 ± 13.3 (18 – 82)	
Weight (kg)	92.9 ± 23.0 (40 – 204)	
Height (cm)	172.6 ± 10.1 (141 – 203)	
N (%)		
Sex	Male	803 (66.3)
	Female	409 (33.7)
Race	White	1097 (90.5)
	Black	48 (4.0)
	Other	67 (5.5)

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Subject Characteristics and Main Criteria for Inclusion:

Subjects were adult male and female volunteers 18 years of age or older and in good general health as determined by the principal investigator. Subject had a clinical diagnosis of psoriasis for at least 6 months as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the investigator. Subject had stable plaque psoriasis for at least 2 months before Screening and at Baseline visits as determined by subject interview of his/her medical history. Subject had moderate to severe plaque psoriasis defined by $\geq 10\%$ body surface area involvement at the Baseline visit. Subject had a PASI score of ≥ 12 and had a Physician's Global Assessment of at least moderate disease at the Baseline visit. Females of childbearing potential were not pregnant or breast-feeding and were practicing an acceptable method of birth control.

Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:

Information pertaining to the adalimumab and placebo formulations used in this study is presented in the following table.

	Formulations	
	Placebo	Adalimumab
Dosage Form	Injectable Solution	Injectable Solution
Strength	0 mg in 0.8 mL	40 mg in 0.8 mL
Concentration	0 mg/mL	50 mg/mL
Mode of Administration	Subcutaneous	Subcutaneous
Bulk Lot / Article Number	08137HK/17102415 08138HK/17102415	13191HK/17102427, 21244HK/17102427 15207HK/17102427, 25272HK/17102427

Duration of Treatment: 52 weeks (16 weeks of Period A, 17 weeks of Period B and 19 weeks of Period C).

Methods of Evaluation:

Pharmacokinetics and AAA: All individual serum adalimumab and AAA concentrations at Baseline, Week 16, Week 33 and Week 52 were tabulated. Summary statistics for adalimumab concentrations stratified by treatment group were calculated for subjects who completed each period.

Population Pharmacokinetics Analyses (NONMEM Analyses): Adalimumab concentration data from this study were combined with the data from Study M02-528, and population pharmacokinetic analyses were performed to estimate adalimumab apparent clearance (CL/F) and apparent volume of distribution (V/F). The structure of the starting pharmacokinetic model was based on the final model obtained in the analysis of the data from Study M02-528. Adalimumab clearance was the pharmacokinetic parameter of primary interest, and volume of distribution was of secondary interest. Population pharmacokinetic models were built using a non-linear mixed-effect population modeling approach with the Non-Linear Mixed Effect Modeling (NONMEM) software and NMTRAN pre-processor.

Results/Discussion:**Pharmacokinetics:**

Summary statistics of adalimumab concentrations for Periods A, B and C are presented in the following table.

Week 16 (End of Period A and Start of Period B)			
	Placebo (N = 355)	Adalimumab (N = 783)	
N	337	752	
Mean	0.000	5.202	
SD	0.000	4.639	
Min	0.000	0.000	
Median	0.000	4.553	
Max	0.000	47.532	
CV%	--	89	
Week 33 (End of Period B and Start of Period C), Trough Concentrations			
	Adalimumab (N = 23)	Adalimumab (N = 550)	
N	21	525	
Mean	3.139	5.216	
SD	2.549	4.225	
Min	0.000	0.000	
Median	2.631	4.509	
Max	7.895	21.590	
CV%	81	81	
Week 52 (End of Period C)			
	Adalimumab (N = 18)	Placebo (N = 184)	Adalimumab (N = 227)
N	17	165	211
Mean	3.990	0.142	6.147
SD	2.678	0.229	4.286
Min	0.000	0.000	0.000
Median	4.719	0.000	5.782
Max	8.964	1.357	20.533
CV%	67	161	70

The mean steady-state trough concentrations of adalimumab (5 µg/mL) observed in subjects with psoriasis during treatment with sc adalimumab 40 mg every other week (eow) as monotherapy were similar to that observed in subjects with rheumatoid arthritis (5 µg/mL). The subjects who received placebo, adalimumab and adalimumab in Periods A, B and C, respectively, had a slightly lower mean trough concentration (3 µg/mL). However, the number of subjects in this group was very small (N = 21), and the lower mean may reflect the typical variability of the data.

AAA:

A total of 825 subjects received at least one dose of adalimumab and had at least one AAA sample taken after the first adalimumab dose (*i.e.*, AAA samples taken on the day of first adalimumab dose or before were not counted). Among these 825 subjects, 73 (8.8%) subjects tested AAA+ at least once during the 52-week treatment period.

Population Pharmacokinetics Analyses (NONMEM Analyses):

The final model was a one-compartment model with first-order absorption and elimination, including inter-individual error terms on CL/F and V/F, the effects of weight, race, age and study on CL/F and the effect of weight on V/F, and a power function as residual error.

The median CL/F of adalimumab was 21 mL/h. This value is similar to that observed in subjects with rheumatoid arthritis treated with adalimumab 40 mg eow as monotherapy (24 mL/h). This is consistent with the observation that the mean trough concentration of adalimumab (5 µg/mL) observed in subjects with psoriasis were similar to those observed in subjects with rheumatoid arthritis (5 µg/mL).

The median V/F of adalimumab was 11.3 L in subjects with psoriasis, which is comparable to that observed in rheumatoid arthritis (11.2 L).

Clearance tended to increase with increasing body weight. Body weight, as a univariate, accounted for 19% of the overall variability in adalimumab clearance. However, the median CL/F increased less than two fold from the first to the fourth weight quartile, while the weight increased about three fold from the first to the fourth weight quartile. The effect of the weight on CL/F was consistent with the observation that adalimumab concentrations were doubled in subjects from the lowest weight quartile compared to those from the highest weight quartile.

Study was a significant covariate on clearance, with the median CL/F value in Study M03-656 being 60% higher than that in Study M02-528. This may be due to the differences in study design.

Study M02-528 was a short term study (12 weeks) with early sampling time points, while Study M03-656 lasted for one year and had later and more sparse sampling time points. Because of the longer observation period of Study M03-656, the potential impact of immunogenicity on adalimumab pharmacokinetics could be greater.

Race and age were also significant covariates on clearance. However, as univariates, they only accounted for 0.01% and 0.9% of the overall variability in adalimumab clearance, respectively.

AAA was not a significant covariate for clearance, probably due to the large variability in the clearance values for AAA- subjects. The range of clearance values for AAA- subjects spanned that for AAA+ subjects, therefore, NONMEM was unable to distinguish the two subpopulations. However, AAA+ subjects did have higher η values (η is the difference between the true value for each individual and the typical value for the population), and the presence of AAA more than doubled the clearance of adalimumab, consistent with what has been observed in studies in rheumatoid arthritis.

There was also a trend for V/F to increase with increasing body weight. Body weight, as a univariate, accounted for 29% of the overall variability in adalimumab V/F. Additionally, there was a 30% difference in median V/F values between the first and fourth weight quartiles, and the average weights in the first and fourth quartiles differed three-fold.

Impact of Immunogenicity on Efficacy:

At Week 16, AAA+ subjects had a statistically significantly lower PASI 75 response rate than AAA- subjects (11% vs. 76%, $p < 0.001$, non-responder imputation). During Period C, the 'event' (i.e., loss of adequate response) rate was higher in AAA+ subjects than that in AAA- subjects (43% vs. 28% for the eow/eow/placebo group [$p = 0.388$], and 18% vs. 4% for the eow/eow/eow group [$p = 0.034$]).

Overall, the results suggest that AAA development reduced the efficacy of adalimumab in subjects with psoriasis, consistent with the higher clearance and hence, reduced adalimumab exposure in the presence of AAA.

Impact of Immunogenicity on Safety:

The overall percentage of subjects with any adverse event (AE) was lower in AAA+ subjects (63.0%) than that in AAA- (78.4%) subjects. There were three serious AEs reported in the AAA+ group. Two of them were considered by the investigator to be not related to study drug (meningioma in the pituitary region and ventricular tachycardia), and the third was considered by the investigator to be probably not related to study drug (deep vein thrombosis). Additionally, there was no suggestion for an underlying mechanism that these events may be caused by AAA.

The AAA+ subjects had a lower incidence of injection site reactions compared to the AAA- subjects.

In conclusion, there was no indication that there were any differences in safety between adalimumab-treated subjects who developed AAA vs. those who did not.

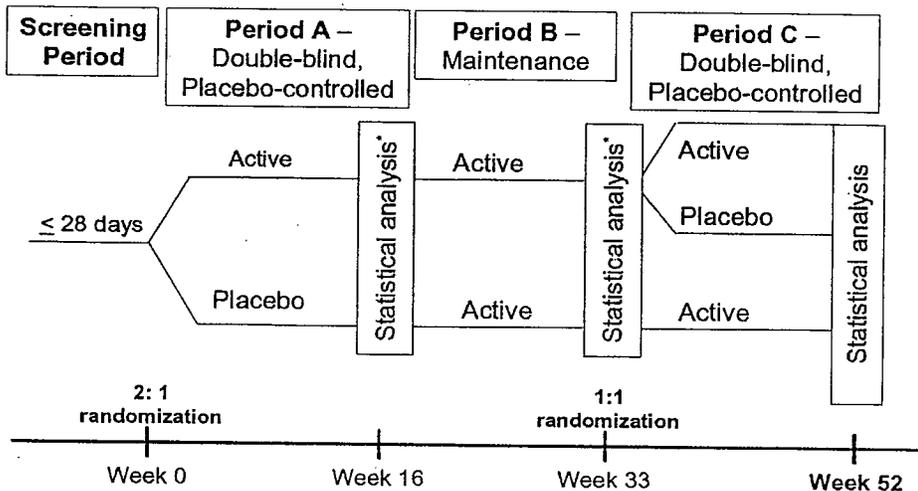
Conclusion:

The mean steady-state trough concentration of adalimumab was 5 $\mu\text{g/mL}$ in subjects with psoriasis. The AAA+ rate was 8.8%.

The median CL/F of adalimumab was 21 mL/h and the median V/F was 11.3 L. Significant covariates included weight, race, age and study on CL/F and weight on V/F. Although AAA was not a significant covariate, the presence of AAA more than doubled the clearance of adalimumab.

Overall, the results suggest that AAA development reduced the efficacy of adalimumab, consistent with the reduced adalimumab exposure in the presence of AAA. There was no indication that there were any differences in safety between adalimumab-treated subjects who developed AAA vs. those who did not.

StudyM03-656: Study Design (Scheme 2)



* PASI 75 responders or better continue in the study

Reviewer's Comments:

The study was reviewed and found acceptable. Please see the clinical pharmacology review text for details.

BLA125057/89 for Humira SC Injectable Solution

Appendix 4.3

Cover Sheet and OCP Filing Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	BLA125057/110	Brand Name	Humira
OCP Division (I, II, III)	DCP III	Generic Name	Adalimumab
Medical Division	GI and Dermatology	Drug Class	Biologics
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	Moderate to Severe Chronic Plaque Psoriasis
OCPB Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	Injectable
		Dosing Regimen	80 mg on Week0 and 40 mg every other week
Date of Submission	03/23/07	Route of Administration	Subcutaneous
Estimated Due Date of OCPB Review	11/27/07	Sponsor	Abbott
Medical Division Due Date	11/2/107	Priority Classification	Standard (10 months)
PDUFA Due Date	01/21/08		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	2	2	One Phase2 and one Phase3 with PK Data
Dose proportionality -	X			
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X			One Phase2 and one Phase3 with PK Data
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2	2	
Filability and QBR comments				
	"X" if yes	ts		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. 1. What are the PK characteristics in patients with CPP after SC Injection? 2. What is the incidence rate of AAA development in the CPP patient population and how does it compare with other patient populations? 3. Did immunogenicity have impact on efficacy? 4. Did CPP patients who had medical history of PsA have higher rate of immunogenicity for AAA+ development?		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	Tien-Mien Chen, Ph.D. 04/23/07			
Secondary reviewer Signature and Date	Sue-Chih Lee, Ph.D. 04/23/07			