2.0 Synopsis

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

Title of Study: A Phase 2 Multicenter Extension Study of the Safety and Efficacy of Adalimumab (D2E7) in Subjects with Moderate to Severe Chronic Plaque Psoriasis

Investigators:

Multicenter

Coordinating Investigator: [redacted] M.D., [redacted] redacted information 25Sep2014

Study Sites:

Multicenter (18 study sites in the United States (US) [13 sites] and Canada [5 sites]).

Publications:

None

Studied Period (Years):	**Phase of Development:** 2
Initiation Date: 11 Mar 2003 (first enrolled subject screened in the lead−in study, Study M02-528)	
Completion Date: 17 Jun 2004 (last subject's final study visit)	

Objectives:

The objectives of this study were to investigate the long-term clinical efficacy and safety of adalimumab in chronic plaque psoriasis subjects who completed 12 weeks of the lead-in study, Study M02-528, and who continued therapy for an additional 48 weeks with subcutaneous (sc) injections of adalimumab.

Methodology:

This was a continuation trial of adalimumab in subjects with moderate to severe chronic plaque psoriasis who successfully completed the double blind, placebo-controlled, 12-week lead-in study, Study M02−528. All study weeks in this protocol were given the 'x' designation to differentiate the visits in this continuation study, Study M02-529, from the visits that occurred in the lead-in study, Study M02−528 (Study M02-529 Week 0x = Study M02-528 Week 12). All subjects who successfully completed the lead-in study, Study M02-528, and who met the inclusion criteria and did not meet the exclusion criteria of this study, Study M02-529, received active therapy. Subjects who received adalimumab in Study M02-528 continued to receive their previously assigned M02-528 dose of adalimumab (40 mg every other week [eow] or 40 mg weekly) in this study. Subjects who received placebo previously in Study M02-528 received a loading dose of adalimumab 80 mg on Week 0x of Study M02-529 (synonymous with Week 12 of M02-528) and then adalimumab 40 mg eow beginning

on Week 1x. Drug administration was performed in a blinded fashion as assigned by [redacted] Study medication administration remained blinded until all subjects completed Week 12x. At Week 12x, subjects with ≥ PASI 50 (Psoriasis Area and Severity Index) response (*i.e.*, at least a 50% reduction from Baseline in PASI score) relative to the Study M02-528 Baseline PASI score continued their current therapy for up to an additional 36 weeks. At any time on or after Week 12x of this study, subjects with < PASI 50 response received open-label, weekly adalimumab therapy (rescue subjects). If, after at least eight weeks of weekly therapy, the subject did not achieve ≥ PASI 50 response relative to the Study M02-528 Baseline PASI score, the subject was to be discontinued from Study M02-529.

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The study was conducted at 18 study sites in the US and Canada, and included a blinded 12-week treatment period (Week 0x to Week 12x) and a 36-week open-label treatment period (After Week 12x to Week 48x). A 30-day follow-up visit and a final phone call 70 days from last dose upon completion or termination of subjects who were not eligible or who did not choose to enroll in the extension study, Study M03-658, a long-term safety, tolerability, and efficacy study.

Number of Subjects (Planned and Analyzed):

Planned: 148 subjects

Analyzed: Blinded period (Week 0x to Week 12x): 137 subjects in the Full Analysis Set (received at least one injection of study drug) and 126 in the Per-protocol Set (those in the Full Analysis Set who did not violate predetermined criteria) were analyzed for efficacy and 137 subjects were analyzed for safety. 132 subjects completed the blinded period of the study.

Open-label period (After Week 12x to Week 48x): 132 subjects in the Full Analysis Set (received at least one injection of study drug) for efficacy and 132 subjects were analyzed for safety. 26 subjects entered the rescue portion of the study. 106 subjects completed the open-label period.

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were subjects who successfully completed the lead-in study, Study M02-528. Subjects were males and females ≥ 18 years of age with moderate to severe chronic plaque psoriasis (psoriasis involving at least 5% of total body surface area (BSA) for at least one year). Subjects with erythrodermic psoriasis, generalized pustular psoriasis, or medication induced or exacerbated psoriasis were excluded. Subjects had active disease despite topical therapy, and had not previously received treatment with anti-TNF therapy. Topical psoriasis therapies, phototherapy, and excessive sun exposure or tanning booth use were discontinued for 2 weeks prior to entry of the lead-in study and throughout both the lead-in study and this study. Non-biologic systemic psoriasis therapies and biologic agents were discontinued 4 and 12 weeks prior to entry of the lead-in study, respectively. Investigative chemical agents were discontinued at least 30 days or five half-lives prior to entry of the lead-in study. Subjects did not have other active skin diseases or skin infections that would have interfered with the evaluation of psoriasis. Subjects did not have history of neurologic symptoms suggestive of central nervous system demyelinating disease, history of active tuberculosis or listeriosis, or persistent chronic or active infections requiring hospitalization with intravenous antibiotics, antivirals, or antifungals within 30 days or oral antibiotics within 14 days prior to entry of the lead-in study.

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

Adalimumab 40 mg/0.8 mL sc - Lot number: [redacted]

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Duration of Treatment:

Subjects in the placebo/adalimumab 40 mg eow treatment group received treatment with adalimumab for up to 48 weeks in this study. Subjects in the adalimumab 40 mg eow and adalimumab 40 mg weekly treatment groups received adalimumab for up to 60 weeks when duration of treatment in the lead-in study, Study M02-528, and duration of treatment in this study are combined (12 weeks and 48 weeks, respectively).

Reference Therapy, Dose and Mode of Administration, Lot Number:

Placebo 0.8 mL sc - Lot number: [redacted] redacted information 25Sep2014

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the proportion of subjects who achieved clinical response as defined by a ≥ PASI 75 response (*i.e.*, at least a 75% reduction in PASI score relative to the Baseline value of Study M02-528) at Week 12x.

Secondary efficacy variables:

Clinical Response

- The proportion of subjects with a Physician's Global Assessment (PGA of psoriasis) score of "*clear*" or "*almost clear*" at Weeks 12x, 16x, 20x, 24x, 32x, 40x, and 48x
- The proportion of subjects achieving a clinical response defined by ≥ PASI 75/50/90 response at Weeks 0x, 4x, 8x, 12x, 16x, 20x, 24x, 32x, 40x, and 48x compared to Study M02-528 Baseline
- PASI 75/50/90 or greater response rates at any time during the study up to Week 12x
- Change and percent change from Baseline (Study M02-528 Week 0) in PASI total score at Weeks 16x, 20x, 24x, 32x, 40x, an 48x

Duration of Response

- The time from when 50% improvement in PASI is achieved at Week 0x compared to the Study M02-528 Baseline to when 50% improvement in PASI is lost up to and including Week 12x for subjects who achieved PASI 50 response at Week 0x.

Quality of Life

- Change from Study M02-528 Baseline in the Dermatology Life Quality Index (DLQI), SF−36®, Zung Depression scale, and EuroQoL-5D (EQ-5D Index and VAS [visual analogue scale]) at Weeks 12x, 24x, and 48x
- The proportion of subjects with DLQI of zero (proportion of subjects "not at all" affected by their psoriasis)

For subjects who underwent dose escalation, the following endpoints were assessed:

- the proportion of subjects achieving ≥ PASI 50/75/90 response at any time after dose escalation
- the proportion of subjects achieving a PGA of "*clear*" or "*almost clear*" at any time after dose escalation
- time to ≥ PASI 50/75 response after dose escalation

Safety:

Adverse events (AEs) were monitored throughout the study. Standard laboratory evaluations, vital signs determinations, and physical examinations were performed at specified timepoints throughout the study. Electrocardiogram, chest x-ray, and tuberculin (purified protein derivative) test were performed at Screening.

Statistical Methods:

All statistical tests were two-sided and conducted at an $\alpha = 0.05$ level. Descriptive statistics (frequency and percentage, mean, 95% confidence interval of the mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum) were used to describe all data. Cochran-Mantel-Haenszel (CMH) test adjusted for weight category was used for categorical data.

Efficacy:

The primary efficacy analysis was a comparison between the adalimumab 40 mg eow and adalimumab 40 mg weekly treatment groups of the proportion of subjects with ≥ PASI 75 response following 24 weeks of treatment (Week 12x) relative to Baseline (Week 0 of Study M02–528). The aim of the primary efficacy analysis was to determine if these two adalimumab treatment groups were similar in terms of clinical response or if a significant difference existed. The primary efficacy variable was analyzed for the Full Analysis Set (main analysis) as well as for the Per-protocol Analysis Set (supportive analysis, no confirmatory conclusion to be drawn from this analysis). The primary analysis was the comparison between treatment groups by the CMH test adjusted for weight category. Subjects without Week 12x evaluations were classified as not achieving PASI 75 response.

For secondary efficacy analyses, analysis of variance (ANOVA) was used for continuous variables and the CMH test was used for categorical variables to assess results between treatment groups. The ANOVA model included the factors of treatment group and Baseline weight category. A 95% confidence interval was provided for the difference between the adalimumab treatment groups and the placebo treatment group. Time to response data was assessed using the Kaplan-Meier method. For the blinded period of the study, secondary efficacy analyses were performed to assess if there was a difference between the adalimumab 40 mg eow and adalimumab 40 mg weekly treatment groups. No statistical comparison was performed for the open-label period of the study. A supportive analysis of the primary variable was performed using the Last Observation Carried Forward (LOCF) approach to impute missing values.

Safety:

Treatment emergent AEs and serious adverse events (SAEs) were summarized by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) AE coding dictionary (version 4.0). A summary of AEs by severity and relationship to study drug was performed. Changes in laboratory data were described using statistical characteristics and compared between active treatment groups using a one-way ANOVA. Shift tables were provided.

Results: Key demographic characteristics and disease characteristics are summarized below:

Demographic Characteristic	Placebo/ adalimumab 40 mg eow N=47	Adalimumab 40 mg eow N=43	Adalimumab 40 mg weekly N=47
Age (years), mean ± SD	44.4 ± 12.9	45.4 ± 11.8	43.5 ± 13.4
Gender, n (%)			
Male	33 (70.2)	30 (69.8)	33 (70.2)
Female	14 (29.8)	13 (30.2)	14 (29.8)
Race/Ethnicity, n (%)			
White	43 (91.5)	38 (88.4)	42 (89.4)
Asian	2 (4.3)	1 (2.3)	2 (4.3)
Other	1 (2.1)	3 (7.0)	1 (2.1)
Black	1 (2.1)	1 (2.3)	2 (4.3)
Hispanic, n (%)	2 (4.3)	3 (7.0)	4 (8.5)

Disease Characteristics at Study Entry:

Disease Characteristic	Placebo/ adalimumab 40 mg eow N=47	Adalimumab 40 mg eow N=43	Adalimumab 40 mg weekly N=47
Psoriasis duration (years), mean ± SD	19.01 ± 9.55	20.99 ± 13.00	18.26 ± 10.77
Baseline PASI, mean ± SD	16.0 ± 7.5	16.5 ± 6.9	14.6 ± 7.7
Baseline PASI, n (%)			
< 12	17 (36.2)	10 (23.3)	18 (38.3)
12-20	19 (40.4)	20 (46.5)	20 (42.6)
> 20	11 (23.4)	13 (30.2)	9 (19.1)
% BSA psoriasis, mean ± SD	28.0 ± 18.0	28.8 ± 15.9	25.0 ± 18.8

Efficacy Results:

Both adalimumab 40 mg eow and adalimumab 40 mg weekly are highly effective in the treatment of subjects with moderate to severe chronic plaque psoriasis. Following 24 weeks of adalimumab treatment (Week 12x), the adalimumab 40 mg eow and adalimumab 40 mg weekly treatment groups were not clinically or statistically different in regard to the proportion of subjects in each group with ≥ PASI 75 response: 67.4% *vs.* 76.6% of subjects, respectively, achieved ≥ PASI 75 response (p = .173) at Week 12x.

Adalimumab demonstrated clinically important improvement in moderate to severe psoriasis as shown by the secondary efficacy endpoints, PGA "*clear*"/"*almost clear*," PASI 50 response, and PASI 90 response. With the exception of ≥ PASI 90, all secondary endpoints in the blinded period of the study were not statistically significantly different between the adalimumab 40 mg eow and adalimumab 40 mg

weekly treatment groups. Overall, these two treatment groups were similar in terms of efficacy. Efficacy results for the placebo/adalimumab 40 eow treatment group following 12 weeks of treatment in this study was comparable to those observed for the 12-week adalimumab 40 mg eow treatment group in Study M02-528.

Adalimumab demonstrated clinically important and statistically significant improvement in the quality of life (QoL) of psoriasis patients as shown by the secondary endpoints of DLQI, EQ-5D (Index and VAS), and SF-36®.

Secondary efficacy results:

	Placebo/ adalimumab 40 mg eow[a]	Adalimumab	
		40 mg eow[b]	40 mg weekly[c]
PGA of "*clear*" or "*almost clear*," n (%)			
Week 12x	21 (44.7)	29 (67.4)	36 (76.6)
Week 48x	25 (54.3)	22 (52.4)	26 (59.1)
≥ PASI 50 response, n (%)			
Week 12x	36 (76.6)	33 (76.7)	40 (85.1)
Week 48x	36 (78.3)	32 (76.2)	33 (75.0)
≥ PASI 75 response, n (%) (Primary Efficacy Endpoint at Week 12x)			
Week 12x	26 (55.3)	29 (67.4)	36 (76.6)
Week 48x	23 (50.0)	28 (66.7)	32 (72.7)
≥ PASI 90 response, n (%)			
Week 12x[d]	15 (31.9)	19 (44.2)	31 (66.0)
Week 48x	19 (41.3)	15 (35.7)	24 (54.5)
≥ PASI 50/75/90 response at any time up to Week 12x, n (%)			
≥ PASI 50 response	43 (91.5)	38 (88.4)	45 (95.7)
≥ PASI 75 response	32 (68.1)	34 (79.1)	41 (87.2)
≥ PASI 90 response	15 (31.9)	24 (55.8)	34 (72.3)
Mean Change and Mean Percent Change in Total PASI Score at Week 48x			
N	38	35	33
Change	-13.7	-13.3	-14.0
% change	-82.2	-82.6	-93.3

a. Week 12x N=47, Week 48x N=46

b. Week 12x N=43, Week 48x N=42

c. Week 12x N=47, Week 48x N=44

d. p=.030 (CMH test adjusted for Baseline body weight) for comparison of adalimumab 40 mg eow and adalimumab 40 mg weekly (excludes placebo/adalimumab 40 mg eow).

Duration of Response

There were 34 subjects in the adalimumab 40 mg treatment group and 44 in the adalimumab 40 mg weekly treatment group who achieved ≥ PASI 50 response at Week 0x. Among these subjects, 4 (11.8%) in the adalimumab 40 mg eow treatment group and 3 (6.8%) in the 40 mg weekly treatment group lost PASI 50 response on or before Week 12x. The chance to lose PASI 50 response is was lower in the adalimumab 40 mg weekly treatment group (risk ratio: 0.563); however, the adalimumab 40 mg weekly treatment group is not statistically significantly different from the adalimumab 40 mg eow treatment group (p=.4585).

Efficacy Results Following Dose Escalation - Rescue Subjects

Open-label dose escalation in the rescue part of the study resulted in improvement of efficacy endpoints in approximately half of the subjects. It was observed that some subjects receiving adalimumab 40 mg eow who had <PASI 50 response can gain this response and achieve PGA of "*clear*" or "*almost clear*" after treatment with adalimumab 40 mg weekly.

	Placebo/ adalimumab 40 mg eow N=13	**Adalimumab**	
		40 mg eow N=9	**40 mg weekly N=4**
	n (%)		
Proportion of Subjects Achieving >= PASI 50/75/90 Response at Any Time			
≥ PASI 50	8 (61.5)	4 (44.4)	0
≥ PASI 75	3 (23.1)	2 (22.2)	0
≥ PASI 90	1 (7.7)	0	0
Proportion of Subjects Achieving PGA of "*Clear*" or "*Almost Clear*" at Any Time			
PGA "*clear*"/"*almost clear*"	5 (38.5)	2 (22.2)	0
Median Time (day) to >= PASI 50/75 Response			
PASI 50	57.0 (29.0, 57.0)	50.0 (29.0, -)	NA
PASI 75	197.0 (113.0, -)	196.0 (168.0, 224.0)	NA

NA: Not applicable. No one in the adalimumab 40 mg weekly treatment group achieved PASI 50 or PASI 75.

Patient-Reported Outcome Results:

Overall, adalimumab continued to be effective in improving QoL of moderate to severe chronic plaque psoriasis subjects after up to 60 weeks of treatment as demonstrated by the secondary endpoints of the DLQI, EQ-5D Health Questionnaire, and SF-36® Health Status Survey (Physical Health Component Summary [PCS] and Mental Health Component Summary [MCS]).

	Adalimumab 40 mg eow[a]	Adalimumab 40 mg weekly[b]
	Mean (95% CI)[c]	Mean (95% CI)[c]
Change from Baseline in DLQI		
Week 12x	-8.8 (-12.9, -4.7)	-10.3 (-14.3, -6.2)
Week 48x	-11.4 (-13.5, -9.3)	-12.1 (-14.7, -9.5)
Change from Baseline in SF-36®		
PHC		
Week 12x	1.6 (-4.1, 7.3)	5.3 (-0.3, 10.9)
Week 48x	3.4 (0.2, 6.6)	6.6 (3.1, 10.2)
MHC		
Week 12x	5.6 (0.4, 10.9)	4.3 (-0.9, 9.4)
Week 48x	6.4 (1.9, 11.0)	5.3 (1.3, 9.2)
Change from Baseline in EQ-5D		
Index		
Week 12x	0.195 (0.040, 0.350)	0.211 (0.057, 0.364)
Week 48x	0.205 (0.119, 0.291)	0.220 (0.114, 0.325)
VAS		
Week 12x	9.3 (-2.4, 21.0)	6.4 (-5.1, 18.0)
Week 48x	13.5 (6.0, 21.0)	13.4 (5.1, 21.7)

Subjects with Total DLQI Score of Zero (Observed Data)			
	Placebo/ adalimumab 40 mg eow N=47	**Adalimumab**	
		40 mg eow N=43	**40 mg weekly N=47**
Week 12x[d]	12 (26.1)	16 (38.1)	23 (53.5)
Week 48x	17 (44.7)	12 (34.3)	19 (57.6)

PHC: Physical Health Component Summary; MCS: Mental Health Component Summary

a. Week 12x N=43, Week 48x N=42

b. Week 12x N=47, Week 48x N=44

c. Mean = least square mean adjusted for weight strata: Mean and corresponding 95% CI are from an ANOVA model.

d. p=.0341 upon comparison of the adalimumab 40 mg eow and adalimumab 40 mg weekly treatment groups.

Safety Results:

Adalimumab was well tolerated in subjects with moderate to severe chronic plaque psoriasis when administered up to 60 weeks:

The number (%) of subjects who reported a treatment-emergent AE was similar between the adalimumab 40 mg eow and adalimumab 40 mg weekly treatment groups (69.8% *vs.* 61.7%, respectively) during the blinded period and the open-label period (73.8% *vs.* 79.5%, respectively). A total of 59.6% and 58.7% of subjects from the placebo/adalimumab 40 mg eow treatment group reported an AE during the blinded period and the open-label period, respectively.

AEs that occurred at a rate of ≥ 5% in any treatment group are shown below by study period. Most treatment-emergent AEs were mild to moderate in severity and not related to study drug.

Blinded Period			
	Placebo/adalimumab 40 mg eow[a]	**Adalimumab**	
		40 mg eow[b]	**40 mg weekly[c]**
MedDRA Preferred Term		**n (%)**	
Headache NOS	1 (2.1)	2 (4.7)	4 (8.5)
Muscle strain	0	1 (2.3)	3 (6.4)
Back pain	0	0	3 (6.4)
Upper respiratory tract infection NOS	0	2 (4.7)	3 (6.4)
Nasopharyngitis	1 (2.1)	5 (11.6)	2 (4.3)
Blood triglycerides increased	2 (4.3)	4 (9.3)	1 (2.1)
Open-label Period			
Nasopharyngitis	2 (4.3)	7 (16.7)	5 (11.4)
Upper respiratory tract infection NOS	5 (10.9)	2 (4.8)	4 (9.1)
Bronchitis NOS	0	3 (7.1)	2 (4.5)
Upper respiratory tract infection viral NOS	3 (6.5)	1 (2.4)	3 (6.8)
Dermatitis contact	0	3 (7.1)	1 (2.3)
Back pain	3 (6.5)	1 (2.4)	1 (2.3)

a. Week 12x N=47, Week 48x N=46

b. Week 12x N=43, Week 48x N=42

c. Week 12x N=47, Week 48x N=44

One death occurred; relationship was not related to adalimumab treatment. SAEs were few and were most commonly assessed as probably not related or not related to adalimumab treatment by the Investigator. Two subjects in the adalimumab 40 mg eow group and 7 subjects in the adalimumab 40 mg weekly group reported a total of 9 SAEs. No SAEs were reported by subjects in the placebo/adalimumab 40 mg treatment group. Just one SAE (malignant melanoma/site/stage unspecified) was considered possibly related to study drug by the Investigator. Very few subjects reported treatment-

emergent AEs of melanomas, malignant neoplasm, and injection site reaction or discontinued prematurely from the study due to an AE.

No serious infectious treatment-emergent AEs were reported during the study. [redacted] redacted information 25Sep2014 For the open-label period of the study, the number (%) of subjects who reported nonserious infectious AEs was 39.1%, 45.2%, and 50.0% (placebo/adalimumab 40 mg eow, adalimumab 40 mg eow, and adalimumab 40 mg weekly, respectively). All non-serious infectious treatment-emergent AE were considered at least probably related to treatment with study drug by the Investigator. The infectious AEs reported are easily medically manageable.

No events of lymphoma, drug-induced lupus, or demyelination were observed during the study.

One subject experienced a positive tuberculin test (possibly related to study drug), which led to discontinuation from the study. The subject was a hospital employee who demonstrated a positive test result upon routine tuberculin testing as part of his job.

Opportunistic infections were infrequent and included one subject with coccidioidomycosis (not related to study drug), 3 subjects with fungal infection NOS (not related to study drug), one subject with staphylococcal infection NOS (not related to study drug), and 3 subjects with herpes simplex (2 possibly related, 1 not related to study drug).

Likewise, reports of malignancy were few: one subject experienced gastric cancer NOS (probably not related to study drug) and two subjects experienced malignant melanoma site/stage unspecified (1 probably not related, 1 possibly related to study drug). All three subjects were discontinued from the study.

Evaluation of laboratory changes did not demonstrate any relevant clinical differences in treatment regimens. Elevations in ALT or AST in subjects with normal values at Baseline were Grade 2 or less, in general were isolated occurrences, were not considered clinically relevant, and in nearly all cases did not lead to drug discontinuation. One subject who received adalimumab had slightly elevated ALT and AST at study entry and was discontinued due to increased liver enzymes.

Summary:

This continuation study demonstrated that adalimumab at both doses (80 mg loading dose + 40 mg eow or two 80 mg loading doses + 40 mg weekly) studied is similarly effective in the long-term treatment (up to 60 weeks) of adult subjects with moderate to severe chronic plaque psoriasis.

Adalimumab at the 40 mg eow or 40 mg weekly dose was effective in treating moderate to severe chronic plaque psoriasis in adult patients with no clinical difference was observed between the two treatment groups. Adalimumab reduced the signs and symptoms of psoriasis and improved QoL in this patient population. The efficacy of adalimumab in psoriasis was evaluated by assessing specific aspects of the disease using recognized endpoints: PASI, PGA, and QoL (DLQI, EQ-5D, SF-36®).

The safety results from this study also demonstrated that adalimumab was well tolerated.

Conclusions:

The results of this study demonstrate that long-term treatment (up to 60 weeks) with adalimumab 40 mg eow or 40 mg weekly is highly effective, improves QoL, and is well tolerated in the treatment of adult subjects with moderate to severe chronic plaque psoriasis.