2.0 Synopsis

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

Title of Study: A Double-Blind, Placebo-Controlled, Multicenter Study of the Efficacy and Safety of Adalimumab in Pediatric Subjects with Enthesitis Related Arthritis

Investigator: Prof. Rubén Burgos-Vargas, MD, [redacted]

Study Sites: 16 study sites in Canada, France, Germany, Italy, Mexico, Poland, Spain, Sweden, and Switzerland

Publications: 1 article

Studied Period (Years): First Subject First Visit: 22 September 2010 Last Subject Last Visit: 30 December 2015 (date of last 70-day follow-up call)	**Phase of Development:** 3

Objectives:

The objectives of this study were to evaluate the efficacy and safety of adalimumab given subcutaneously (SC) every other week (eow) as compared with placebo in pediatric subjects with enthesitis-related arthritis (ERA) and to examine the pharmacokinetics (PK) and immunogenicity of adalimumab following SC administration in this subject population.

Methodology:

This was a Phase 3, double-blind (DB), placebo-controlled, multicenter study with an open-label (OL) period conducted in Canada, Mexico, and Europe in pediatric subjects with ERA who were at least 6 years but less than 18 years of age at Baseline. Approximately 45 pediatric patients with ERA were planned to be enrolled.

The study included a 30-day Screening Period, a 12-week DB placebo-controlled treatment period with an early escape option, and an OL adalimumab eow treatment period with a maximum duration of 192 weeks, and a follow-up phone call 70 days after the last dose of adalimumab.

The blinded study period began at the Baseline visit and ended at the Week 12 visit. Subjects who met enrollment criteria were randomized in a 2:1 ratio to receive either adalimumab (body surface area [BSA] dosing 24 mg/m^2 up to a maximum of 40 mg) eow or matching placebo via SC injection. An early escape option at Weeks 4 and 8 was provided for subjects who either experienced a worsening of disease or failed to improve.

Methodology (Continued):

For subjects who completed the blinded period, the OL period began at the Week 12 visit. For subjects who met the criteria for early escape, the OL period began at the Week 4 or Week 8 visit (depending on when the criteria were met). During the OL period, each subject received OL adalimumab eow for a maximum of 192 weeks or until adalimumab received country and local (if applicable) regulatory approval for ERA and all applicable local reimbursement procedures were completed. Subjects not continuing on adalimumab after the end of the study had a 70-day follow-up phone call to obtain follow-up information on any new or ongoing adverse events (AEs).

Each subject in the study was planned to have a maximum of 204 weeks of treatment.

Number of Subjects (Planned and Analyzed):

Planned: 45 subjects

Analyzed: 46 subjects

Two analysis sets were used for the efficacy analyses and 2 for the safety analyses:

1. 46 subjects (intent-to-treat [ITT] analysis set – defined as all randomized subjects who received at least 1 dose of study drug. The ITT analysis set was analyzed as randomized and was used for the primary analyses of efficacy, as well as demographics, baseline characteristics, medical history, and previous/concomitant medications.
2. 41 subjects (per-protocol [PP] analysis set) – subjects in the ITT analysis set after excluding those subjects with major protocol deviations. The identification of major protocol deviations was done before unblinding and before the database lock. The PP set was used to evaluate the impact of major protocol deviations on the results of the study.
3. 46 subjects (safety analysis set) – all subjects who were randomized and received at least 1 dose of study drug (adalimumab or placebo). Safety analyses were based on the actual treatment received by subjects, irrespective of treatment group assignment. No subjects were excluded from the safety analysis set.
4. 46 subjects (any adalimumab set) – all subjects who received at least 1 dose of adalimumab were analyzed for safety from the first dose of adalimumab onwards.

Diagnosis and Main Criteria for Inclusion:

- Subjects 6 to < 18 years of age with diagnosis of ERA as defined by the International League of Associations for Rheumatology (ILAR) prior to subject's sixteenth birthday
- At least 3 active joints (swelling not due to deformity or joints with loss of motion [LOM] + pain and/or tenderness)
- Evidence of enthesitis in at least one location (either documented in the past or present at Baseline
- Inadequate response or intolerance to at least 1 nonsteroidal anti-inflammatory drug (NSAID). In addition, subject must also have had inadequate response or intolerance to at least 1 disease-modifying anti-rheumatic drug (DMARD), either sulfasalazine (SSZ) or methotrexate (MTX). Subjects who had a contraindication to SSZ or MTX use could be enrolled in the study
- Subjects could not have a diagnosis of any ILAR juvenile idiopathic arthritis (JIA) subtype other than ERA
- Subjects could not have had previous biologic therapy, including anti-tumor necrosis factor (TNF) therapy with a potential impact on pediatric ERA

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

Adalimumab 40 mg/0.8 mL, vial

Bulk Lot Number: 09-022029, 10-005219, 10-005326, 11-005881, 13-001150, 14-007022

Duration of Treatment: 204 weeks

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

Placebo for adalimumab 0.8 mL, vial

Bulk Lot Number: 09-024593, 11-000422

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness).

Ranked secondary efficacy variables analyzed at Week 12 were:

1. Number of sites of enthesitis
2. Tender joint count (TJC) for 72 joints
3. Swollen joint count (SJC) for 68 joints
4. American College of Rheumatology (ACR) Pediatric (Pedi)30 response
5. ACR Pedi50 response
6. ACR Pedi70 response

Other supportive efficacy variables that represent the effect of adalimumab on multiple components of active ERA were assessed during the DB and OL periods of the study.

Safety:

AEs, physical examination, vital signs, and laboratory data were assessed throughout the study.

Statistical Methods

Efficacy:

Efficacy analyses were conducted on the ITT analysis set and the PP analysis set. Analyses on the ITT analysis set were primary. In the efficacy analyses, missing or incomplete data were handled using last observation carried forward (LOCF) as the primary method for continuous variables, nonresponder imputation (NRI) as the primary method for dichotomous variables, and as observed cases and LOCF as sensitivity analyses.

The primary efficacy variable was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness).

The primary confirmatory analysis was done using an analysis of covariance (ANCOVA) model adjusting for the number of active joints at Baseline at alpha level of 0.05. For subjects who did not have an active joint count at Week 12 or who had escaped early to OL treatment, their last available joint count from the DB period was used.

For the comparison of secondary endpoints between the 2 treatment groups, Fisher's exact test was used for discrete variables, and 1-way ANOVA was used for continuous endpoints. Results in the OL period were reported stratified by the treatment the subject was randomized to in the DB period and overall.

Long term effectiveness of adalimumab during the OL period was analyzed using descriptive statistics, overall and by treatment allocation in the double-blind period.

Statistical Methods (Continued)

Pharmacokinetic:

PK results and conclusions are presented in a separate PK report ([redacted]).

Safety:

Treatment-emergent AEs (TEAEs) were summarized by treatment group using descriptive statistics. TEAEs were defined as events with an onset date on or after the first dose of study drug and up to 70 days after the last dose of study drug.

All AEs discussed in this report are TEAEs unless otherwise noted. A TEAE was defined as follows:

- DB period (through Week 12)
  - For subjects who discontinued prematurely from the DB period, TEAEs were defined as any event with an onset date that was on or after the first DB dose of study drug and with an onset date no more than 70 days after the last dose of DB study drug
  - For subjects who continued into the OL period, TEAEs were defined as any event with an onset date that was on or after the first DB dose of study drug and with an onset date that was on or before the day prior to the date of the first OL dose of study drug.
- Any adalimumab: TEAEs were defined as any event with an onset date that was on or after the first dose of adalimumab and with an onset date no more than 70 days after the last dose of adalimumab.

AEs were tabulated by system organ class and preferred term, whereby, the most current implemented Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 18.0) was used. Also, summaries by severity and relationship to study drug were done. Certain AEs, such as serious, severe, or leading to premature withdrawal, were listed and described in detail. AEs of special interest for treatment with biologics were defined in the statistical analysis plan (SAP) and analyzed separately.

Other safety variables, such as laboratory data, were described by descriptive statistics. In addition, shift tables and listings were provided for abnormal values, whereby, the normal range of the analyzing laboratory was used.

Summary/Conclusions

Efficacy Results:

Study M11-328 evaluated the efficacy of adalimumab 40 mg eow compared to placebo for 12 weeks and up to Week 156 of the OL period in 46 subjects with ERA. All 46 randomized subjects received at least 1 dose of study drug.

Seventeen subjects discontinued from the study, all during the OL period; 4 of these subjects discontinued due to sustained remission. Seven subjects (3 randomized to placebo, 4 randomized to adalimumab) early escaped from the DB period to the OL period.

The majority of subjects in the ITT analysis set were male and white; mean age was 12.9 years. Subjects reported having had symptoms of ERA for a mean of 2.6 years and had been diagnosed with ERA for a mean of 1.9 years prior to Baseline. A total of 91.3% of subjects previously used DMARDs for their ERA, 100.0% previously used NSAIDs, and 56.5% previously used corticosteroids. No statistically significant differences were observed between treatment groups. Results were similar in the PP analysis set.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Primary Endpoint

The primary efficacy variable was mean percent change from Baseline to Week 12 in the number of active joints with arthritis, which was achieved in favor of adalimumab with mean percent decrease of –62.6% in subjects in the adalimumab group compared to –11.6% in subjects in the placebo group (*P* = 0.039; LOCF). This finding was supported by sensitivity analyses using as observed data (–83.3% versus –32.1%; P = 0.018), non-parametric methods (medians –88.9% versus –50.0%, *P* = 0.025 [ITT, LOCF]; medians –90.9% versus –58.3%, *P* = 0.038 [PP, LOCF]), and numerically, but not statistically significant improvement observed in the PP analysis set (–66.0% versus –30.2%, *P* = 0.093 [LOCF]).

Percent Change from Baseline at Week 12 in Number of Active Joints with Arthritis (ITT and PP)

	Placebo		Adalimumab		Between Group Difference		
Week 12	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**Difference**	**95% CI**	***P* Value[a]**
Primary analysis							
ITT (LOCF)	15	–11.6 ± 100.5	31	–62.6 ± 59.53	–51.17	–99.69, –2.66	0.039
Sensitivity analysis							
ITT (as observed)	12	–32.1 ± 100.72	27	–83.3 ± 24.85	–51.58	–93.60, –9.55	0.018
PP (LOCF)	14	–30.2 ± 72.38	27	–66.0 ± 57.29	–36.00	–78.31, 6.30	0.093

a. *P* value for difference between treatment groups from ANCOVA with treatment group and number of active joints at Baseline in the model.

Sensitivity Analyses for Percent Change from Baseline at Week 12 in Number of Active Joints with Arthritis using Non-Parametric Testing (ITT and PP)

	Placebo				Adalimumab				
Week 12	**N**	**Mean ± SD**	**Median (Q1, Q3)**	**Mean Wilcoxon Score**	**N**	**Mean ± SD**	**Median (Q1, Q3)**	**Mean Wilcoxon Score**	***P* Value[a]**
ITT (LOCF)	15	–11.6 ± 100.50	–50.0 (–76.2, 66.7)	29.67	31	–62.6 ± 59.53	–88.9 (–100.0, –55.0)	20.52	0.025
PP (LOCF)	14	–30.2 ± 72.38	–58.3 (–76.2, 25.0)	26.21	27	–66.0 ± 57.29	–90.9 (–100.0, –66.7)	18.30	0.038

a. *P* value from exact two-sample Wilcoxon test.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Ranked Secondary Variables

Results for number of sites of enthesitis, TJC, SJC, ACR Pedi30 response, and ACR Pedi50 response were numerically superior in favor of adalimumab; however, results for the 6th ranked secondary efficacy variable, ACR Pedi70 response, reached statistical significance at Week 12. Given the small sample size in this study, the positive trends observed support the efficacy of adalimumab in the ERA patient population.

Mean Change from Baseline and Responder Status at Week 12 for Ranked Secondary Variables (ITT)

Ranked Variables 1 through 3 (LOCF)

Variable / Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline: Mean ± SD	Change from Baseline: Median (Min to Max)	Between Group Difference: Difference[b]	95% CI[c]	*P* Value[d]
1. Number of sites of enthesitis								
Placebo	15	7.8 ± 7.49	5.1 ± 8.92	–2.7 ± 4.98	–4.0 (–12.0 to 11.0)	--	--	--
Adalimumab	31	8.3 ± 8.89	3.9 ± 6.60	–4.4 ± 6.20	–3.0 (–22.0 to 12.0)	–1.62	(–5.32, 2.08)	0.382
2. TJC for 72 joints								
Placebo	15	11.9 ± 9.34	7.5 ± 8.06	–4.5 ± 8.97	–7.0 (–19.0 to 13.0)	--	--	--
Adalimumab	31	13.4 ± 10.49	5.5 ± 8.77	–7.9 ± 8.25	–6.0 (–28.0 to 8.0)	–3.40	(–8.78, 1.97)	0.209
3. SJC for 68 joints								
Placebo	15	5.2 ± 3.69	2.8 ± 2.83	–2.4 ± 4.66	–3.0 (–11.0 to 5.0)	--	--	--
Adalimumab	31	6.7 ± 7.30	3.2 ± 7.27	–3.5 ± 5.61	–3.0 (–19.0 to 9.0)	–1.12	(–4.49, 2.26)	0.509

Ranked Variables 4 through 6 (NRI)

	N	Responder	Non-Responder	Difference[b]	95% CI[e]	*P* Value[f]
4. ACR Pedi30						
Placebo	15	9 (60.0)	6 (40.0)	--	--	--
Adalimumab	31	22 (71.0)	9 (29.0)	11.0	–18.5, 40.5	0.514
5. ACR Pedi50						
Placebo	15	6 (40.0)	9 (60.0)	--	--	--
Adalimumab	31	21 (67.7)	10 (32.3)	27.7	–2.0, 57.5	0.111
6. ACR Pedi70						
Placebo	15	3 (20.0)	12 (80.0)	--	--	--
Adalimumab	31	17 (54.8)	14 (45.2)	34.8	8.1, 61.6	0.031

a. Only subjects with both Baseline and visit values are shown.
b. Difference of adalimumab minus placebo.
c. 95% CI for difference of adalimumab minus placebo.
d. *P* value for differences between treatment groups from 1-way ANOVA.
e. 95% CI based on normal approximation.
f. *P* value for differences between treatment groups from Fisher's exact test.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Other supportive efficacy variables that represent the effect of adalimumab on multiple components of active ERA were assessed during the 12-week DB period, as well as additional OL data available through Week 156. While few of these variables achieved statistical significance in favor of adalimumab at Week 12, the majority demonstrated trends in favor of adalimumab with results being sustained or improving further during the OL period.

Safety Results:

No deaths were reported during the study. During the DB period, a greater percentage of subjects who received adalimumab (21/31, 67.7%) reported at least 1 AE compared with subjects who received placebo (8/15, 53.3%). The most frequently reported AEs (reported by ≥ 2 subjects in any treatment group) included upper respiratory tract infection, headache, gastroenteritis, injection site pain, nausea, alanine aminotransferase (ALT) increased, abdominal pain upper, and syncope. All AEs were considered mild or moderate in severity by the Investigator and most subjects (n = 16) reported AEs that were considered by the Investigator to be not related or probably not related to study drug. Nine subjects in the adalimumab treatment group reported possibly or probably related AEs compared to 4 subjects in the placebo group. Two serious AEs (SAEs) were reported by 1 subject in the adalimumab treatment group (abdominal pain upper and headache).

All subjects who received at least 1 dose of adalimumab at any time during the study experienced at least 1 AE. Of the most frequently reported AEs (reported by ≥ 3 subjects), upper respiratory tract infection, nasopharyngitis, headache, diarrhea, gastroenteritis, JIA (worsening of ERA), pharyngitis, and pharyngotonsillitis were reported in > 15% of subjects. Seven subjects in the any adalimumab set reported at least 1 severe AE (disseminated tuberculosis [TB]; latent TB; pustular psoriasis [Ps]; JIA [worsening of ERA]; second degree burns and third degree burns [in the same subject]; blood pressure increased and weight increased [in the same subject]; and diffuse vasculitis, pneumonia, and JIA [worsening of ERA, in the same subject]). Twenty-nine subjects reported AEs that were considered possibly or probably related to study drug by the Investigator.

Ten subjects reported a total of 19 SAEs. Six SAEs in 5 subjects were considered by the Investigator to be possibly or probably related to the study drug (upper abdominal pain and headache [in the same subject], disseminated TB, appendicitis, urinary tract infection, and diffuse vasculitis). The remaining events were considered probably not or not related to study drug by the Investigator. Six SAEs were considered severe by the Investigator (disseminated TB, second degree burns, third degree burns, JIA [worsening of ERA], diffuse vasculitis, and pneumonia); all other SAEs were considered mild or moderate in severity. Seven subjects prematurely discontinued due to AEs, all during or following OL treatment (disseminated TB; Ps; JIA [worsening of ERA] and pain; dermatitis allergic; pustular Ps, injection site pain and injection site pruritus; and diffuse vasculitis and congestive heart failure [CHF]).

Summary/Conclusions (Continued)

Safety Results (Continued):

None of the following events of special interest were reported during the study: Legionella infection, reactivation of hepatitis B, opportunistic infection, oral candidiasis; progressive multifocal leukoencephalopathy, malignancies (including lymphoma, nonmelanoma skin cancer, melanoma, heptatosplenic T-cell lymphoma, and leukemia), lupus-like syndrome, demyelinating disease, hematologic events, diverticulitis, intestinal perforation, intestinal stricture, pulmonary embolism, interstitial lung disease, adalimumab error-related events and maladministration, Stevens-Johnson Syndrome, erythema multiforme, pancreatitis, sarcoidosis, autoimmune hepatitis, reversible posterior leukoencephalopathy syndrome, or amyotrophic lateral sclerosis.

- Infection: During the DB period, a greater proportion of subjects in the adalimumab group reported at least 1 treatment-emergent infection (9/31, 29.0%) compared with the placebo group (3/15, 20.0%). Infections reported in 2 or more subjects included upper respiratory tract infection, gastroenteritis, and paronychia. All other infections during the DB period were reported by no more than 1 subject each. Among subjects who received at least 1 dose of adalimumab at any time during the study, 41 out of 46 subjects (89.1%) reported at least 1 treatment-emergent infection. The most frequently reported infections were upper respiratory tract infection, nasopharyngitis, gastroenteritis, pharyngitis, and pharyngotonsillitis, with all other infections being reported by no more than 5 subjects each. All infections were nonserious events with the exception of infections in 4 subjects (disseminated TB, appendicitis, urinary tract infection, and pneumonia). One subject reported a parasitic infection (acarodermatitis, placebo group, DB period) considered by the Investigator to be not related to study drug.
- TB: One subject reported a SAE of active TB (disseminated TB, OL period), which led to discontinuation of study drug and was considered as probably related to study drug by the Investigator. Two subjects reported treatment-emergent latent TB in the OL period. One event was a nonserious event of latent TB that was considered probably related to study drug by the Investigator. The other event was an SAE of positive tuberculin test that was considered to be probably not related to study drug by the Investigator.
- Allergic reactions: Three subjects reported nonserious allergic reactions (asthma, injection site urticaria, and rash, all during the OL period). The injection site urticaria was considered probably related to study drug by the Investigator; the asthma and rash were considered not related and probably not related, respectively.
- Vasculitis: One subject experienced 2 events of treatment-emergent vasculitis. The subject experienced an event of nonserious vasculitis (OL period) that was considered possibly related to study drug by the Investigator. No systemic symptoms were reported in conjunction with this event. This subject also experienced a serious event of diffuse vasculitis (posttreatment following OL period) that was considered probably related to study drug.
- Cardiovascular events: One subject experienced a serious event of CHF (posttreatment following the OL period), which was considered probably not related to study drug.
- Worsening or new onset Ps: Two subjects reported nonserious events of worsening or new onset Ps (both during the OL period). One subject experienced a new onset Ps, which was considered possibly related to study drug by the Investigator and one subject experienced pustular Ps, which was considered probably related to the study drug by the Investigator.

Summary/Conclusions (Continued)

Safety Results (Continued):

- Liver event: One subject experienced a nonserious liver event (hepatocellular injury, adalimumab group, DB period). The event was considered not related to study drug by the Investigator.
- Injection site reaction: During the DB period, 3 subjects in the adalimumab group reported an injection site reaction compared to 1 subject in the placebo group. Among subjects who received at least 1 dose of adalimumab, 7 subjects (15.2%) reported an injection site reaction. All injection site reactions were considered by the Investigator as mild in severity and all were probably or possibly related to study drug with the exception of 1 event.

While 6 subjects had common terminology criteria for AEs (CTCAE) toxicity grade ≥ 3 hematology or clinical chemistry value during the study, all were considered not clinically meaningful, and with the exception of 1 subject who continued to have mildly elevated ALT, all resolved by the last visit for each subject. Mean changes from Baseline to final vital signs values were overall small and not clinically significant and shifts from normal to high or low final vital signs values were infrequent and not clinically meaningful.

Conclusions:

Study M11-328 met the primary endpoint of mean percent change from Baseline to Week 12 in the number of active joints with arthritis, showing a mean percent decrease of 62.6% in the adalimumab group compared to a decrease of 11.6% in subjects in the placebo group ($P = 0.039$; LOCF). Of the ranked secondary variables, the more stringent ACR Pedi70 response (the 6th ranked secondary variable) was statistically significant in favor of adalimumab, with the remaining ranked secondary variables showing numerically, but not statistically significant, greater improvement in signs and symptoms of ERA with adalimumab compared to placebo. Additional efficacy variables, while not generally statistically significant, also demonstrated overall trends for improvement in subjects receiving adalimumab when compared to subjects receiving placebo. These results demonstrate that adalimumab is an effective treatment for reducing the signs and symptoms of ERA and for sustained efficacy up to 156 weeks.

Adalimumab was generally safe and well tolerated; the safety profile observed throughout the study over 204 weeks of therapy was consistent with previous clinical trials for adalimumab, and no new safety signals were observed.