# 2.0 Synopsis

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

**Title of Study:** Compassionate Use Study of Adalimumab in Children 2 to < 4 Years Old or Age 4 and Above Weighing Less Than 15 kg with Active Juvenile Idiopathic Arthritis (JIA)

**Investigator:**
Daniel J. Kingsbury, MD
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**Study Sites:** 14 study sites in the US, France, Czech Republic, and Germany

**Publications:** 6

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| **Studied Period (Years):**<br>First Subject First Visit: 24 March 2009<br>Last Subject Week 24 Visit: 21 March 2013 | **Phase of Development:** 3b |

**Objectives:** The primary objective of this study was to evaluate the safety of adalimumab in subjects 2 to < 4 years of age and subjects ≥ 4 years of age who weighed < 15 kg with moderately to severely active polyarticular JIA or polyarticular course JIA. The secondary objectives of this study were to collect pharmacokinetic (PK) data and to evaluate the effectiveness of adalimumab in these subjects.

**Methodology:** This was an open-label (OL) multicenter study for subjects 2 to < 4 years of age and subjects ≥ 4 years of age and weighing < 15 kg diagnosed with moderately to severely active polyarticular JIA or polyarticular course JIA, per International League of Associations for Rheumatology (ILAR) criteria, treated in a clinical setting with adalimumab. Measurements of the subject's height and weight were used to determine the subject's dose of adalimumab. All subjects had a Screening visit, Baseline visit, and visits at Weeks 2, 4, 8, 12, 16, 20, and 24. Visits beyond Week 24 occurred every 12 weeks for those subjects who continued in the study. Serum samples were collected for PK analyses (including anti-adalimumab antibody [AAA] analysis).

**Number of Subjects (Planned and Analyzed):**
Planned: 30
Actual: 32

**Diagnosis and Main Criteria for Inclusion:**

- A parent or guardian had voluntarily signed and dated an informed consent form, approved by an institutional review board/independent ethics committee, after the nature of the study was explained and the subject's parent or legal guardian had the opportunity to ask questions. The informed consent was signed before any study-specific procedures were performed or before any medication was discontinued for the purpose of this study. The parent was to have been willing to comply with all the requirements of this study protocol.
- Subject had a disease diagnosis of moderately to severely active polyarticular or polyarticular course JIA (defined as arthritis affecting ≥ 5 joints at the time of treatment initiation). This corresponded to the ILAR categories of polyarticular rheumatoid factor positive (RF+), polyarticular rheumatoid factor negative (RF–), and extended oligoarthritis disease.
- Subject must have been aged 2 to < 4 years old at Screening with moderately to severely active polyarticular JIA or polyarticular course JIA or age ≥ 4 and weighing < 15 kg with moderately to severely active polyarticular JIA or polyarticular course JIA.
- Subject was judged by the investigator to be in generally good health on the basis of medical history, laboratory profile, and physical examination performed at Screening and confirmed at Baseline. This included, but was not limited to, a normal cardiopulmonary and normal neurological examination result.
- Parent or legal guardian had to be able and willing to administer subcutaneous (SC) injections or have a qualified person available to administer SC injections.
- Parent or legal guardian had to be willing to actively supervise storage and administration of adalimumab and had to ensure that the time of each dose was accurately recorded in the subject's diary.
- Subject must have had a negative purified protein derivative (PPD) test (or equivalent) at Screening. If subject had a positive (≥ 5 mm induration) PPD test result, a chest x-ray (CXR; posterior-anterior and lateral views) was to be performed. If subject had a positive test (or equivalent), had a past ulcerative reaction to PPD placement, and/or a CXR consistent with tuberculosis exposure, subject was not to be enrolled into the study.
- For subjects in the European Union (EU), subject must have previously failed, had an insufficient response to, or been intolerant to ≥ 1 disease-modifying anti-rheumatic drug.

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

United States (US)/Puerto Rico: Adalimumab 20 mg/0.4 mL in prefilled syringes (bulk lot numbers: [redacted])

EU: Adalimumab 40 mg/0.8 mL in single-use vials (bulk lot numbers: [redacted]) redacted information 07Aug2014

The dose of adalimumab was 24 mg/m$^2$ body surface area up to a total dose of 20 mg adalimumab administered every other week as a single dose by SC injection.

**Duration of Treatment:** In the US/Puerto Rico, at the completion of 24 weeks, subjects could continue in the study until they reached 4 years of age and ≥ 15 kg. In the EU, at the completion of 24 weeks, subjects could continue for a maximum of 1 year after they reached 4 years of age and ≥ 15 kg to allow transition to an appropriate treatment.

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

None

**Criteria for Evaluation**

**Efficacy (Secondary Endpoints):**

- Pediatric American College of Rheumatology (PedACR) response
- Joint assessments (swollen and tender joint count, limitation of passive motion, pain on passive motion, and active joint count)
- Parent's Global Assessment of subject's disease activity (100 mm visual analogue scale [VAS])
- Parent's Assessment of Pain (VAS)
- Physician's Global Assessment (PGA) of Disease Activity (VAS)
- Disability Index of Childhood Health Assessment Questionnaire (DICHAQ) – physical function
- Child Health Questionnaire (CHQ)-PF50
- C-reactive protein (CRP)

**Pharmacokinetic:** Serum concentrations of adalimumab were measured for each subject who consented to this procedure and summary statistics were computed for each sampling time. Serum AAA concentrations were determined and the impact of AAA on serum adalimumab concentrations, efficacy, and safety were analyzed. [redacted]

**Safety (Primary Endpoint):** The primary endpoint of the study was the incidence of serious adverse events (SAEs) and adverse events (AEs) reported over the course of the study. All AEs were collected from the start of study drug administration and all SAEs were collected from the time the subject signed the study-specific informed consent. AEs and SAEs were collected over the course of the study until 70 days following the last injection of adalimumab, if subjects terminated the study, and before the start of commercial adalimumab or other biologic.

**Statistical Methods**

**Efficacy:** PedACR30/50/70/90 response was defined as ≥ 30%/50%/70%/90% improvement in at least 3 of the 6 JIA core set variables and ≥ 30%/50%/70%/90% worsening in not more than 1 of the 6 JIA core set criteria. Improvement of the core set of variables by ≥ 30%/50%/70%/90% was defined as a percent change from Baseline ≤ –30 and worsening of a core set of variables by ≥ 30%/50%/70%/90% was defined as a percent change from Baseline ≥ 30. The proportion of subjects achieving a PedACR30/50/70/90 response was assessed with counts and percentages.

Change from Baseline for joint assessments, PGA of Disease Activity, Parent's Global Assessment of Disease Activity, Parent's Global Assessment of Pain, DICHAQ – physical function, CHQ-PF50, and CRP were summarized by number of subjects, mean, standard deviation, first quartile, median, third quartile, minimum, and maximum.

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**Statistical Methods (Continued)**

**Safety:** Safety analyses of treatment-emergent and pre- and post-treatment SAEs and AEs were carried out using the safety population, which included all subjects who received ≥ 1 dose of study drug. Treatment-emergent AEs (TEAEs) were defined as AEs that began either on or after the first dose of the study drug and no more than 70 days after the last dose of the study drug. Subjects who began commercial adalimumab before the end of the study were to receive a follow-up phone call prior to the first dose of commercial adalimumab. The number and percent of subjects experiencing AEs and the event rate per 100 patient- years were tabulated by body system and Medical Dictionary for Regulatory Activities preferred term. In addition, AEs were summarized by maximum severity and maximum relationship to study drug. AEs that were serious, severe, or led to death or premature discontinuation from the study were described in detail and listed by subject.

Mean change from Baseline in hematology and chemistry laboratory parameters and vital signs were summarized by number of subjects, mean, standard deviation, and median value. Shifts from Baseline in laboratory and liver function test parameters to lower or higher ranges were also summarized. The last evaluation prior to the first dose of study drug was used as Baseline for all analyses. Laboratory determinations meeting the Common Toxicity Criteria ≥ grade 3, clinically-significant liver function tests, and clinically-significant vital signs were listed by subject.

**Summary/Conclusions**

**Efficacy Results:**

Study M10-444 was a Phase 3b OL study designed to evaluate safety, and secondarily, efficacy, of adalimumab in subjects 2 to < 4 years of age and subjects ≥ 4 years of age weighing < 15 kg, with moderately to severely active polyarticular JIA or polyarticular course JIA. A total of 32 subjects were enrolled at 14 sites in the US, France, the Czech Republic, and Germany. The majority of subjects were female and white, with a mean age of 3.0 ± 0.723 years and mean weight of 13.4 ± 1.96 kg. Baseline disease activity was consistent with moderately to severely active JIA and the largest proportion of subjects was diagnosed with either sero-negative polyarthritis (type 2 JIA) or extended oligoarthritis (type 5 JIA).

Responses for efficacy variables demonstrated that adalimumab (dose determined by body surface area) administered subcutaneously every other week reduced JIA disease activity in this population. A PedACR30/50 response was achieved by at least 80% of subjects from Week 12 through Week 120. At Week 12, the majority of subjects achieved a PedACR70 and at least one-third of subjects achieved a PedACR90. A decrease in mean change from Baseline was observed for all joint assessments, including TJC75, SJC66, POM75, LOM69, and AJC73 and the mean change from Baseline was highest from Week 60 through at least Week 84. A decrease in mean change from Baseline was observed for the health and quality of life assessments, Parent's Global Assessment of subject's disease activity, Parent's Assessment of Pain, and PGA of Disease Activity, from Week 12 through Week 120 and the largest mean changes (range from –42.6 to –47.7 mm) occurred from Week 72 through Week 120. A decrease in mean change from Baseline was observed for the physical function component of the DICHAQ from Week 12 through Week 120 and the largest mean change from Baseline (–0.9) occurred at Week 72 and Week 84.

**Summary/Conclusions (Continued)**

**Efficacy Results (Continued):**

Mean change from Baseline increased at Week 12 for all categories of the CHQ-PF50 and the greatest increase was observed for physical functioning, role/social limitations/emotional/behavioral, role/social limitations – physical, and bodily pain/discomfort. The categories that demonstrated the greatest increase overall were global health, physical functioning, role/social limitations – physical, bodily pain/discomfort, and parental impact – emotional. Lastly, a decrease in the mean change from Baseline was observed for CRP from Week 12 through Week 84 and CRP levels decreased to within the normal range at Week 72 and Week 84. All results starting at Week 72 and continuing through Week 120, however, should be interpreted with caution because the number of subjects had declined during those weeks.

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**Safety Results:** No deaths occurred during this study. Greater than 90% of subjects (217 events, 481.2 E/100PYs) reported at least 1 TEAE and 2 subjects who experienced a nonserious flare of juvenile arthritis discontinued from study drug. The TEAEs most frequently reported by at least 5% of subjects were nasopharyngitis, pyrexia, bronchitis, cough, rhinorrhea, upper respiratory tract infection, juvenile arthritis, otitis media, and vomiting. The majority of subjects reported TEAEs that were considered by the investigator to be not related or probably not related to study drug. The majority of subjects experienced TEAEs that were considered by the investigator to be mild to moderate in severity. A total of 6 subjects (18.8%) experienced severe TEAEs and include uveitis, otitis media, platelet count decreased*, Type 1 diabetes mellitus, arthritis, and juvenile arthritis. The subject that experienced a juvenile arthritis flare was discontinued from study drug; the event was considered by the investigator to be probably related to study drug. The other severe events were considered by the investigator to be not related or probably not related to study drug.

Of the special interest AES that were examined, a total of 25 subjects (78.1%) reported at least 1 treatment-emergent infection during the study. The most frequently reported infections that were at least possibly related to study drug were nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, gastroenteritis, and rhinitis. The majority of subjects who reported an infection experienced events that were considered by the investigator to be mild or moderate in severity and not related or probably not related to study drug. Three subjects had serious infections and these events were considered by the investigator to be mild to moderate in severity and not related to study drug. No subjects prematurely discontinued from study drug as a result of an infection. A total of 4 subjects reported treatment-emergent injection site reaction-related events. These events were considered by the investigator to be mild in severity and probably related to study drug. The events resolved and the subjects continued in the study. Two subjects reported an allergic reaction-related TEAE that included one event of rash that was considered by the investigator to be possibly related to study drug and one event of intermittent urticaria that was considered to be not related to study drug. Both events were considered mild in severity. Two subjects reported a treatment-emergent hematologic disorder during the study, both of which were considered to be not related to study drug. One subject reported an event of microcytic anemia that was considered by the investigator to be mild in severity and 1 subject reported a decreased platelet count that was considered by the investigator to be severe. The event of decreased platelet count was considered resolved after a repeat test was performed by a local hospital laboratory and the results for platelet count were within normal range.

* A repeat platelet count was performed by a local hospital laboratory and the results were within normal range.

**Summary/Conclusions (Continued)**

**Safety Results (Continued):**

Mean change from Baseline in hematology and chemistry laboratory values was generally small and clinically unremarkable. Shift trends were observed for subjects who had a low or normal chemistry laboratory value for ALT (7.1% of subjects), AST (21.4% of subjects), alkaline phosphatase (3.6% of subjects), blood urea nitrogen (14.3% of subjects), inorganic phosphate (6.9% of subjects), calcium (42.3% of subjects), sodium (6.7% of subjects), glucose (31.0% of subjects), albumin (23.3% of subjects), total protein (13.3% of subjects), cholesterol (26.7% of subjects), triglycerides (26.7% of subjects), and CRP (33.3% of subjects) that shifted to a high value. One subject had a high or normal eosinophil count that shifted to a low value. Clinically significant abnormalities were observed in hematology values for 3 subjects and in chemistry values for 2 subjects. These subjects developed a common toxicity criteria grade ≥ 3 value for a single laboratory measurement that resolved before the end of the study. Two subjects had clinically significant liver function tests, 1 of which resolved before the end of the study. Both subjects had received methotrexate concomitantly. None of the subjects discontinued early from the study because of their abnormal values. No shifts were observed in bilirubin, anti-adalimumab antibodies, or anti-double-stranded DNA values.

The mean change from Baseline in heart rate and body temperature was within normal range for children 2 – 4 years of age. There was a 5.63 ± 1.55 kg mean change from Baseline in weight, indicating the subjects were growing. The incidence of potentially clinically significant vital signs for pulse rate of ≤ 50 bpm or a decrease in pulse rate of ≥ 15 bpm from Baseline was 56.3%. The incidence of potentially clinically significant vital signs for pulse rate of ≥ 120 bpm or an increase in pulse rate of ≥ 15 bpm from Baseline was 65.6%. In most cases, the abnormal values were intermittent. A total of 9 subjects had potentially clinically significant decreases and 8 subjects had potentially clinically significant increases at the final determination. No subjects discontinued from study drug because of abnormal vital signs.

**Conclusions:** The data presented in this clinical study report demonstrate that adalimumab therapy up to 120 weeks was effective for treatment of moderately to severely active polyarticular or polyarcticular course JIA in subjects 2 to < 4 years of age or age ≥ 4 weighing < 15 kg. Adalimumab administered subcutaneously eow was generally safe and well-tolerated in these populations and the safety profile throughout the study was consistent with profiles in older pediatric patients with JIA from previous adalimumab clinical trials. No new safety signals were observed. In addition, adalimumab dosing, based on the height and weight of young children, was feasible and appropriate for this population.