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# Patient-Reported Outcomes Among Patients Ages Two to Seventeen Years With Polyarticular-Course Juvenile Idiopathic Arthritis Treated With Subcutaneous Abatacept: Two-Year Results From an International Phase III Study

Nicolino Ruperto,[1] Daniel J. Lovell,[2] Alberto Berman,[3] Francisco Ávila-Zapata,[4] Gerd Horneff,[5] Maria Alessio,[6] Mara L. Becker,[7] Alexandre Belot,[8] Ruben Burgos-Vargas,[9] Maria L. Gamir,[10] Claudia Goldenstein-Schainberg,[11] Iloite M. Scheibel,[12] Maria T. Terreri,[13] Lawrence Zemel,[14] Joe Zhuo,[15] Margarita Askelson,[15] Robert Wong,[15] Alberto Martini,[16] and Hermine I. Brunner,[2] for the Pediatric Rheumatology Collaborative Study Group and the Paediatric Rheumatology International Trials Organisation

**Objective.** To describe longitudinal changes in patient-reported outcomes (PROs) in children with polyarticular-course juvenile idiopathic arthritis (pJIA) treated with subcutaneous abatacept.

**Methods.** Secondary analysis of a single-arm, open-label 24-month study of patients ages 6–17 years and 2–5 years. PROs included Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI), parent global assessment of child well-being (PaGA), pain assessment, and Activity Limitation Questionnaire (ALQ). Clinical outcomes included 50% or greater improvement in JIA American College of Rheumatology (ACR) criteria, clinically inactive disease, and Juvenile Arthritis Disease Activity Score.

**Results.** For the 6- to 17-year-old (n = 173) and 2- to 5-year-old (n = 46) cohorts, respectively, median (Q1, Q3) changes from baseline in CHAQ-DI at months 4 and 24 were –0.3 (–0.8, 0.0) and –0.5 (–1.0, –0.1), and –0.4 (–0.8, 0.0) and –0.5 (–1.0–-0.1). Median pain scores were below cutoff threshold for clinically relevant pain (<35 mm) by month 1 (6 to 17 years, 32.3 mm; 2 to 5 years, 25.7 mm), reaching a nadir at month 24 (6 to 17 years, 6.0 mm; 2 to 5 years, 2.0 mm). For the 6- to 17-year-old and 2- to 5-year-old cohorts, respectively, median PaGA scores were 47.8 (n = 172) and 42.1 (n = 46) at baseline and 6.3 (n = 107) and 2.0 (n = 37) at month 24. In both cohorts, ALQ components improved from baseline to month 4 and were largely maintained to month 24. Clinical outcomes improved through to month 24.

**Conclusion.** Early and sustained PRO improvements were reported in this phase III, open-label trial of subcutaneous abatacept in patients with pJIA.

## INTRODUCTION

The term juvenile idiopathic arthritis (JIA) encompasses a heterogeneous group of chronic pediatric rheumatic conditions of unknown etiology presenting in children <16 years of age (1–4). Children with JIA often have poor functional ability and quality of life because of disability and pain associated with this chronic disease (5,6). Patient-reported outcomes (PROs) can augment clinical data and provide valuable information on a patient's quality of life and the aspects of disease that are important to the patient and caregiver but may not be captured through standard clinical assessments.

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[1]Nicolino Ruperto, MD, MPH: IRCCS Istituto G. Gaslini Clinica Pediatrica e Reumatologia, UOSID Centro Trial, PRINTO, Genova, Italy; [2]Daniel J. Lovell, MD, MPH, Hermine I. Brunner, MD, MSc, MBA: Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio; [3]Alberto Berman, MD: Universidad Nacional de Tucuman, San Miguel de Tucumán, Argentina; [4]Francisco Ávila-Zapata, MD: Hospital Star Medica Merida, Yuc, Mexico; [5]Gerd Horneff, MD: Asklepios Clinical Sankt Augustin, Sankt Augustin, Germany, and University of Cologne, Cologne, Germany; [6]Maria Alessio, MD: Universita di Napoli, Napoli, Italy; [7]Mara L. Becker, MD, MSCE: Duke University School of Medicine, Durham, North Carolina; [8]Alexandre Belot, MD, PhD: Hôpital Femme Mère Enfant, CHU de Lyon, Lyon, France; [9]Ruben Burgos-Vargas, MD: Hospital General de México, Mexico City, Mexico; [10]Maria L. Gamir, MD: Hospital Universitario Ramón y Cajal, Madrid, Spain; [11]Claudia Goldenstein-Schainberg, MD, PhD: Hospital das Clinicas HCFMUSP, Universidade de São Paulo, São Paulo, Brazil; [12]Iloite M. Scheibel, PhD: Grupo Hospitalar Conceição, Porto Alegre, Brazil; [13]Maria T. Terreri, PhD: Universidade Federal de São Paulo, São Paulo, Brazil; [14]Lawrence Zemel, MD: Connecticut Children's Medical Center, Hartford; [15]Joe Zhuo, PhD, Margarita Askelson, MS, Robert

**SIGNIFICANCE & INNOVATIONS**

- Subcutaneous (SC) abatacept treatment was associated with early and clinically meaningful improvements in patient-reported outcomes (PROs) such as disability, pain, overall well-being, and activity of daily living; these improvements were sustained over 2 years.
- Compared with intravenous abatacept, treatment with SC abatacept was associated with improvement in more PROs that are both clinically relevant and stringent in patients with polyarticular-course juvenile idiopathic arthritis (JIA), including those ages 2 to 5 years.
- Treatment with abatacept is associated with better disease control, clinical outcomes, and PROs; the improvements in clinical outcomes support a potential benefit for the use of SC abatacept in very young children with JIA (i.e., those ages 2 to 5 years).

The American College of Rheumatology (ACR) 2019 guidelines recommend initial treatment of polyarticular-course JIA [pJIA; JIA of any category with 5 or more affected joints (7)] with a conventional synthetic disease-modifying antirheumatic drug (csDMARD) such as methotrexate (MTX) (8). In patients with pJIA who have an inadequate response or intolerance to csDMARDs, the use of a biologic (b) DMARD, such as a tumor necrosis factor inhibitor (TNFi), abatacept, or tocilizumab is recommended (8).

Abatacept, a selective T cell co-stimulation modulator, is available in intravenous (IV) and subcutaneous (SC) formulation (9). Two phase III studies have demonstrated the efficacy and safety of both IV and SC abatacept in patients with pJIA and inadequate responses to DMARDs, including TNFis (10–12).

In the phase III study of IV abatacept (10 mg/kg), significant and meaningful improvements were observed in PROs with abatacept compared with placebo in patients ages 6 to 17 years; these improvements were maintained for up to 7 years (13,14). However, there is limited information available regarding patients with pJIA receiving SC abatacept and also patients who are age ≤5 years old. Therefore, the inclusion of children ages 2 to 5 years in the SC abatacept study is of particular importance because treatment of these patients early in their disease course with DMARDs has been associated with better disease control, better clinical outcomes, and improved quality of life through childhood and into adulthood (15,16). The aim of this analysis was to examine the effects of SC abatacept treatment on PROs across the pediatric age range in patients with pJIA.

## PATIENTS AND METHODS

**Study design and interventions.** This analysis includes data from a previously published phase III, single-arm, open-label, international, multicenter, pharmacokinetic end point study composed of 2 age cohorts of patients with pJIA (1 cohort included patients ages 6 to 17 years [6 to 17-year-old cohort] and the other included patients ages 2 to 5 years [2- to 5-year-old cohort]) who were treated with SC abatacept (ClinicalTrials.gov identifier: NCT01844518) (10). Patients received weekly SC abatacept for 4 months based on body weight tier (10 to <25 kg [50 mg], 25 to <50 kg [87.5 mg], and ≥50 kg [125 mg]); the primary end point was the abatacept steady-state serum trough concentration at month 4. After 4 months, patients with a 30% or greater improvement in JIA-ACR criteria (JIA-ACR 30) could continue for an additional 20 months of treatment with open-label SC abatacept. JIA-ACR 30 was defined as a 30% or greater improvement in at least 3 of the 6 JIA-ACR core set variables (number of active joints, number of joints with limitation of motion, physician's global assessment of disease activity, parent global assessment of child well-being [PaGA], functional ability as measured by the cross-culturally adapted and validated version of the Childhood Health Assessment Questionnaire-Disability Index [CHAQ-DI] [17,18], and laboratory measurement of inflammation, as measured by C-reactive protein [CRP] level) and a 30% or greater worsening in 1 or fewer of the remaining JIA-ACR core set variables (19). Patients who did not achieve at least a JIA-ACR 30 response at month 4 were given the option to discontinue treatment or to continue SC abatacept for an additional 3 months and then discontinue treatment if a JIA-ACR 30 response was not achieved by month 7.

Patients were included if they met the International League of Associations for Rheumatology criteria for JIA in 1 of the following categories (2): extended oligoarticular JIA, rheumatoid factor (RF) –positive polyarticular JIA, RF -negative polyarticular JIA, enthesitis-related arthritis, psoriatic arthritis, or systemic JIA (with systemic features absent for ≥6 months before enrollment; ≤10% of the study population). Patients were also required to have a history of 5 or more joints with active disease and active articular disease at baseline, defined as 2 or more active joints and 2 or more joints with limitation of motion at baseline. All patients were naive to treatment with abatacept but may have had an inadequate response or intolerance to 1 or more biologic (limited to ≤30% of the study population, including TNFis) or non-biologic DMARDs. Nonsteroidal antiinflammatory drugs (NSAIDs) or analgesics that do not contain aspirin were permitted in patients who experienced pain that was not adequately controlled by the baseline medications and study drug. To avoid

Wong, MD: Bristol Myers Squibb, Princeton, New Jersey; [16]Alberto Martini, MD: Universita di Genova, Genova, Italy.

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Address correspondence via email to Nicolino Ruperto, MD, MPH, at nicolaruperto@gaslini.org.

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confounding the patients' pain perception at study visits, rescue analgesics and additional NSAIDs were not permitted 12 hours before an evaluation of joints at a study visit. The addition of csDMARDs was permitted during the 20-month long-term extension phase at the investigator's discretion.

**Ethical approval.** The study was conducted in accordance with the Declaration of Helsinki (20), the International Conference on Harmonisation Guidelines for Good Clinical Practice, and local regulations. At each site and before initiation of the study, an institutional review board or independent ethics committee approved the protocol, consent forms, and any other written information provided to patients or their legal representatives. All patients and their legal representatives provided written informed consent.

**PRO assessments.** CHAQ-DI was measured on a 0–3 scale across 8 domains of disability components, with higher values indicating greater disability: no disability, 0; mild disability, 0.1; mild to moderate disability, 0.6; moderate disability, 1.8 (21). The CHAQ-DI end points evaluated included the proportions of patients with minimal clinically important improvement (MCII; –0.2) (22) and absence of disability (CHAQ-DI = 0); only patients with CHAQ-DI scores of >0 at baseline were included in the improvement analysis. The CHAQ-DI MCII was calculated from baseline to each follow-up time point.

Pain and PaGA assessments were measured using a 0 to 100-mm visual analog scale (VAS) with higher values indicating higher pain (cutoff for mild pain, 35 mm) (23) and lower PaGA values indicating reduction in overall well-being, respectively. The proportion of patients with mild pain (pain VAS <35 mm [23]; below the cutoff threshold for clinically relevant pain) was calculated over time. The components of the Activity Limitation Questionnaire (ALQ) ranged from 0 to 30 days with lower values indicating more activity (13). Participation in daily activities for the child were assessed by a parent questionnaire and contained the following questions:

- "In the past 30 days, on how many days did your child's JIA keep him/her from attending school (excluding vacation/holidays)? ___ days"
- "In the past 30 days, on how many days did your child's JIA keep you from doing your usual activities? ___ days"
- "In the past 30 days, on how many days did you pay for child care for your son/daughter with JIA in order for you to engage in your usual activities? ___ days"

PRO measures were reported by parents/caregivers at each study visit (every 4 weeks for 4 months, then every 12 weeks, except for the ALQ [at 2 and 4 months, then every 6 months]) over 24 months and included CHAQ-DI (17,18); the 2 related discomfort scales, pain assessment MCII >10 mm and PaGA MCII reduction <10 mm (23–25) (all post hoc analyses); and the ALQ for parents/caregivers (prespecified exploratory end point developed for the abatacept trial) (13). Outcomes included in the ALQ are the absolute number of missed school or nursery days, the percentage of missed school or nursery days per month relative to an assumed average of 20 days/month, need for paid care, and missed activity time for parent/caregiver.

**Clinical outcome assessments.** Prespecified clinical outcomes over 24 months included JIA-ACR 50, clinically inactive disease (modified ACR criteria; $CID_{ACR}$) (26), and Juvenile Arthritis Disease Activity Score in 71 joints using the CRP level (JADAS71-CRP; cutoff value for low disease activity [LDA]: ≤3.8; inactive disease [$CID_{JADAS}$]: ≤1; and high disease activity: >10.5) (27–30) are reported here.

Effectiveness outcomes for the 6- to 17-year-old cohort, but not the 2- to 5-year-old cohort, have been previously published (10); JIA-ACR response rates and $CID_{ACR}$ for the overall population (both cohorts combined) are shown, including data for the 15 patients in the 2- to 5-year-old cohort that were not available at the time of the original publication (because of incomplete efficacy data at the last time point [day 729]). $CID_{ACR}$ status included 3 variables and was defined as the absence of active joints, physician's global assessment of disease activity of 10 mm or less, and a CRP level of 0.6 mg/dl or less (based on the normal range for CRP as defined by the central analysis site) (26). JADAS71-CRP was calculated for the 2 populations and included a summary of the scores over time. JADAS71-CRP included the following measures: physician's global assessment of disease activity (VAS 0–100 mm, where 0 = no disease activity and 100 = maximum disease activity), PaGA (VAS 0–100 mm, where 0 = very well and 100 = very poor), CRP (normalized on a 0–10 scale), and active joint count with a maximum of 71 active joints (31).

**Statistical analysis.** All efficacy analyses were descriptive, and no formal statistical testing was performed. For all efficacy data and the continuous PRO variables (CHAQ-DI, pain, PaGA, and ALQ item data), an "as observed" (i.e., missing values were not imputed) analysis was conducted. For the proportions of patients with CHAQ-DI MCII, CHAQ-DI = 0, and JIA-ACR, responses were assessed in the intention-to-treat (ITT) population for each cohort, defined as all treated patients (patients with missing data were imputed as nonresponders). Based on the study's main objective and design, there were no formal hypotheses or statistical testing. Efficacy and safety analyses were descriptive within each age cohort except where indicated. Clinical outcomes ($CID_{ACR}$; $CID_{JADAS}$) were analyzed in the ITT population for the 6 to 17-year-old and 2- to 5-year-old cohorts combined. Data for the separate cohorts have been published.

## RESULTS

**Baseline disease characteristics and patient demographic information.** The baseline disease characteristics and patient demographics have been published (10). Briefly, a total of 219 patients entered the study and received the study

drug, of whom 173 were in the 6 to 17-year-old cohort and 46 in the 2 to 5-year-old cohort. A total of 156 patients completed the 20-month extension period; 132 were ages 6 to 17 years, and 24 were ages 2 to 5 years (Figure 1). The baseline PROs, CHAQ-DI, patient pain, PaGA VAS, and individual components of the ALQ were similar between cohorts (Table 1). The median CHAQ-DI (interquartile range) was 0.9 (0.4–1.5) and 1.2 (0.8–1.6) for the 6 to 17-year-old and 2 to 5-year-old cohorts, with 14 and 6 patients, respectively, having CHAQ-DI = 0.

**CHAQ-DI.** Early, clinically meaningful improvements in CHAQ-DI were observed after 2 to 3 months of treatment. The improvements in CHAQ-DI over time were consistent between cohorts; these trends were maintained over 24 months (Figure 2). The percentage of patients who achieved CHAQ-DI MCII at month 4 and month 24 was 57% (n = 99) and 47% (n = 81) in the 6- to 17-year-old cohort and 61% (n = 28) and 59% (n = 27) in the 2- to 5-year-old cohort (Figure 2A). The absence of disability (CHAQ-DI = 0) at month 4 and month 24 was reported in 28% (n = 48) and 26% (n = 45) of patients in the 6- to 17-year-old cohort, respectively (Figure 2B). At baseline, 14% of patients in the 2- to 5-year-old cohort had absence of disability; this increased to 22% (n = 10) and 39% (n = 18) at month 4 and month 24, respectively (Figure 2B). Median CHAQ-DI improved over time in both cohorts (Figure 3A). In the 6- to 17-year-old cohort, the median (Q1, Q3) changes in CHAQ-DI from baseline were –0.3 (–0.8, 0.0) and –0.5 (–1.0, –0.1) at months 4 and 24, respectively. In the 2- to 5-year-old cohort, these values were –0.4 (–0.8, 0.0) and –0.5 (–1.0, –0.1) at months 4 and 24, respectively.

**Pain VAS.** In both cohorts, pain scores decreased early in treatment and improvements continued over time (Figure 3B). On average, mild pain (VAS <35 mm) status was reached as early as month 1 (median pain scores: 6- to 17-year-old cohort, 32.3 mm; 2- to 5-year-old cohort, 25.7 mm), reaching a nadir at month 24 (median pain scores: 6- to 17-year-old cohort, 6.0 mm; 2- to 5-year-old cohort, 2.0 mm). In the 2- to 5-year-old cohort, the proportion of patients with mild pain (VAS <35 mm) increased from 48% at baseline to 59% at month 1 and 74% at month 2; at the end of the study (month 24), 76% of patients had mild pain.

**PaGA VAS.** In both cohorts, improvements (>10 mm) in median PaGA VAS scores were observed early in treatment (6- to 17-year-old cohort, month 1; 2- to 5-year-old cohort, month 2), and continued through month 24 (Figure 3C). For the 6- to 17-year-old and 2- to 5-year-old cohorts, respectively, median PaGA scores were 47.8 (n = 172) and 42.1 (n = 46) at baseline and 6.3 (n = 107) and 2.0 (n = 37) at month 24.

**ALQ.** In the 6- to 17-year-old cohort, the median (Q1, Q3) values for the ALQ components at baseline were absolute numbers of missed school days, 2.0 (0.0–4.0); number of paid care days, 0.0 (0.0–0.0); and number of days of parent/caregiver missed activity, 2.0 (0.0–5.0). In the 2- to 5-year-old cohort, the median (Q1, Q3) values for the ALQ components at baseline were absolute numbers of missed school days, 1.0 (0.0–5.0); number of paid care days, 0.0 (0.0–0.0); and number of days of parent/caregiver missed activity, 3.0 (0.0–7.0). In both

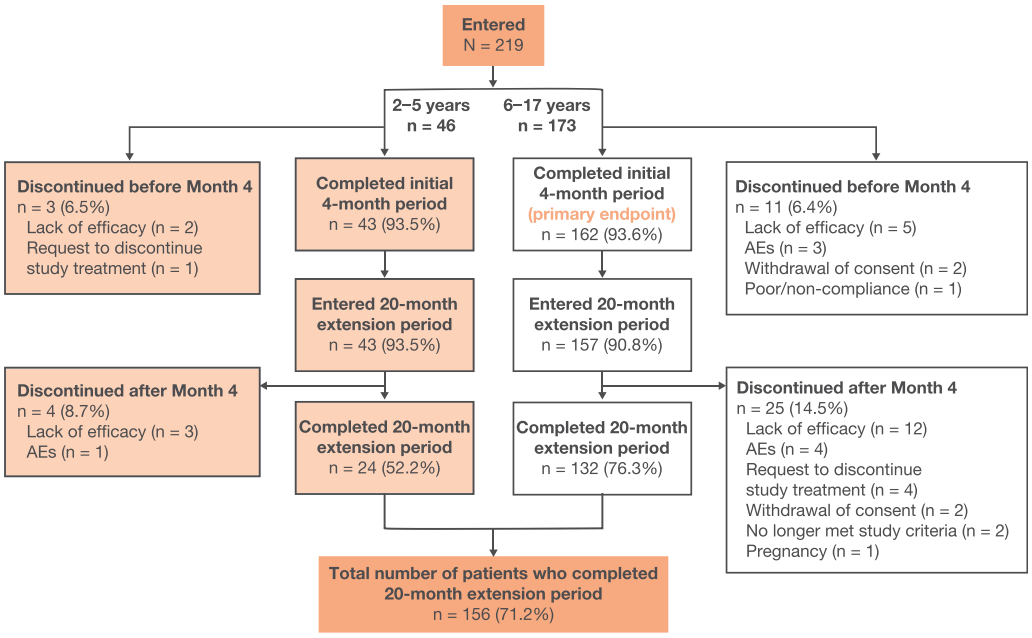


**Figure 1.** Patient disposition. The primary end point was the abatacept steady-state serum trough concentration at month 4. AE = adverse event.

**Table 1.** Baseline demographics and clinical characteristics*

| Characteristics | 6- to 17-year-old cohort (n = 173) | 2- to 5-year-old cohort (n = 46) |
|---|---|---|
| Age, median (IQR) years | 13.0 (10.0–15.0) | 4.0 (3.0–5.0) |
| Female, no. (%) | 136 (78.6) | 28 (60.9) |
| Geographic region, no. (%) | | |
| North America | 22 (12.7) | 0 |
| South America | 56 (32.4) | 8 (17.4) |
| Europe | 78 (45.1) | 36 (78.3) |
| ROW | 17 (9.8) | 2 (4.3) |
| Disease duration, median (IQR) years | 2.0 (0.0–4.0) | 0.5 (0.0–1.0) |
| pJIA disease onset categories, no. (%) | | |
| Polyarthritis RF− | 94 (54.3) | 29 (63.0) |
| Polyarthritis RF+ | 46 (26.6) | 3 (6.5) |
| Extended oligoarthritis | 19 (11.0) | 10 (21.7) |
| Systemic JIA | 5 (2.9) | 0 |
| Undifferentiated or persistent oligoarthritis† | 5 (2.9) | 0 |
| Enthesitis-related arthritis | 4 (2.3) | 0 |
| Psoriatic arthritis | 0 | 4 (8.7) |
| JIA-ACR core set variable, median (IQR) | | |
| Number of active joints | 10.0 (6.0–19.0) | 7.0 (6.0–12.0) |
| Joints with LOM | 8.0 (4.0–15.0) | 8.0 (4.0–11.0) |
| Physician global assessment | 48.0 (31.0–67.0) | 50.0 (35.0–60.0) |
| Parent's global assessment of well-being, VAS, mm‡ | 47.8 (24.1–68.0) | 42.1 (17.9–54.7) |
| CHAQ-DI‡ | 0.9 (0.4–1.5) | 1.2 (0.8–1.6) |
| CRP, mg/dl§ | 0.2 (0.1–0.9) | 0.1 (0.1–1.4) |
| Prior biologic use, no. (%) | 46 (26.6) | 10 (21.7) |
| Baseline MTX use, no. (%) | 136 (78.6) | 37 (80.4) |
| Baseline oral corticosteroid use, no. (%) | 56 (32.4) | 9 (19.6) |
| Months of exposure to SC abatacept, median (range) | 24.3 (1.9–28.0) | 24.1 (4.0–26.2) |
| Pain, VAS, mm | 49.0 (26.5–72.0) | 39.5 (19.6–60.0) |
| ALQ components, median (IQR) | | |
| Number of days of parental/caregiver missed activity | 2.0 (0.0–5.0) | 3.0 (0.0–7.0)¶ |
| Number of paid care days | 0.0 (0.0–0.0)# | 0.0 (0.0–0.0)¶ |
| Number of missed school days | 2.0 (0.0–4.0)# | 1.0 (0.0–5.0)¶ |
| JADAS71-CRP score, median (IQR)** | 21.0 (13.5–30.3) | 18.1 (14.0–23.1) |

* ALQ = Activity Limitation Questionnaire; CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index; CRP = C-reactive protein; IQR = interquartile range; JADAS71-CRP = Juvenile Arthritis Disease Activity Score in 71 joints using the CRP level; JIA-ACR = juvenile idiopathic arthritis-American College of Rheumatology criteria; LOM = limited range of motion; MTX = methotrexate; pJIA = polyarticular-course JIA; RF = rheumatoid factor; ROW = rest of world; SC = subcutaneous; VAS = visual analog scale.
† Protocol violation.
‡ In the 6- to 17-year-old cohort, n = 172.
§ Normal ≤0.6 mg/dl.
# n = 172 and 171 for number of days of paid care days and missed school days, respectively.
¶ n = 45.
** In the 6- to 17-year-old cohort, n = 171.

cohorts, most ALQ components improved from baseline to month 4, with improvements largely maintained over time to month 24 (Table 2). In the 6- to 17-year-old cohort, the proportion of parents/caregivers who reported no missed school days, paid child care days, or parent/caregiver activity days at month 24 (79.0%, 91.4%, and 75.2%, respectively) were improved from those at baseline (41.5%, 84.9%, and 34.7%, respectively). Similarly, in the 2- to 5-year-old cohort, the proportion of parents/caregivers who reported no missed school days, paid child care days, or parent/caregiver activity days at month 24 (81.1%, 91.9%, and 78.4%, respectively) was improved from those at baseline (48.9%, 84.4%, and 40.0%, respectively).

**Clinical outcomes.** The proportion of patients with JIA-ACR 50 responses and $CID_{ACR}$ in the overall patient population (both cohorts combined) increased from baseline through month 21 (Figure 4A; month 24 does not accurately represent the efficacy outcomes in the ITT population at this time point because fewer data were available in the 6- to 17-year-old cohort). Median JADAS71-CRP values were below the cutoff for LDA (≤3.8) by month 7 (Figure 4B).

## DISCUSSION

The primary pharmacokinetic end point, steady-state trough concentration ($C_{minss}$) at day 113, showed that SC abatacept was above the target therapeutic exposure at month 4; this is consistent with the results of this analysis showing improvements in both PROs and clinical outcomes by month 4. In both cohorts, patients improved from moderate disability at baseline to mild disability by

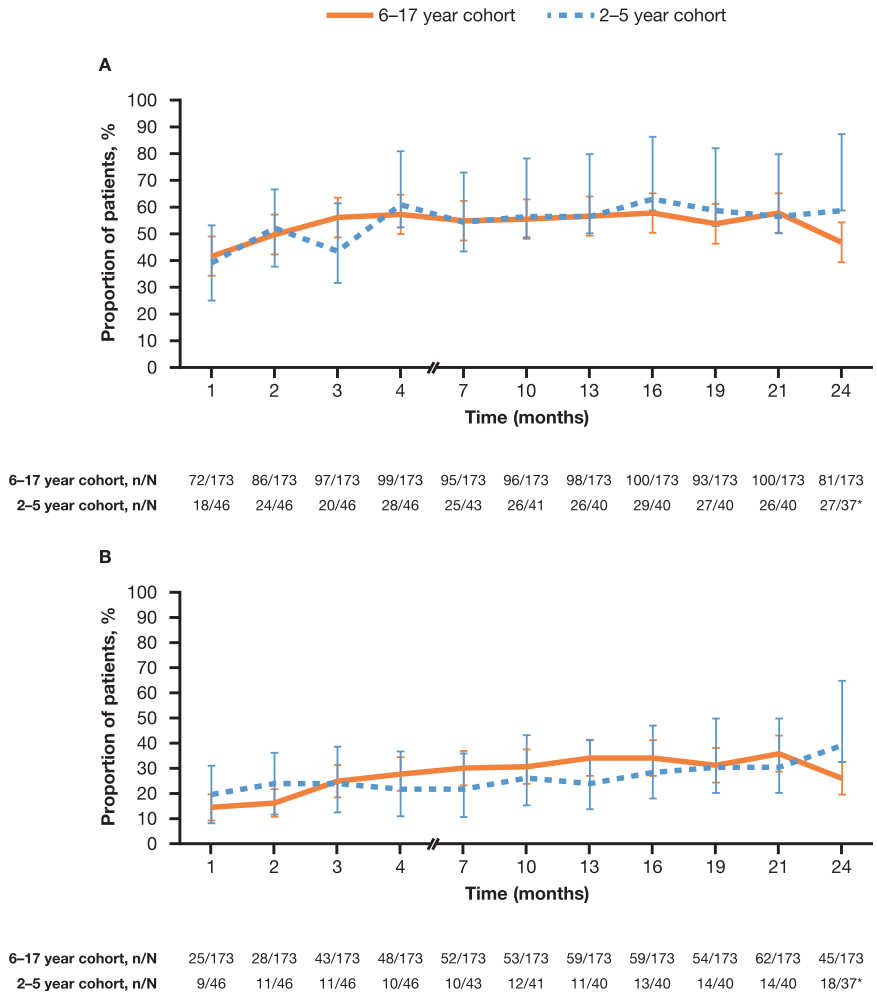


**Figure 2.** Proportions of patients in the 6- to 17-year-old cohort (n = 173) and the 2- to 5-year-old cohort (n = 46) with **A**, Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI) minimal clinically important improvement (CHAQ-DI −0.2) and **B**, absence of disability (CHAQ-DI0) over time. Intention-to-treat analysis (6- to 17-year-old cohort: missing values are imputed as nonresponders throughout the cumulative period; 2- to 5-year-old cohort: missing values are imputed as nonresponders through month 4 and were then "as observed"). Error bars represent 95% confidence intervals. *Data presented for month 24 do not accurately represent the outcomes at this time point because fewer patients had data collected at this visit.

month 24. Similarly, patient pain was reduced early in treatment. These early improvements in PROs and clinical outcomes were maintained over time up to 24 months across both age cohorts.

The results for SC abatacept reported here support those seen in the phase III trial for IV abatacept, in which substantial improvements in PROs (CHAQ-DI, pain, and participation in daily activities) were reported by month 4 and were maintained to month 24 in children with pJIA ages 6 to 17 years (14). The present analysis extends this observation, showing improvements in patients ages 2 to 17 years receiving SC abatacept using different PROs (e.g., ALQ) and PROs that are both clinically meaningful (e.g., CHAQ-DI MCII, pain VAS <35 mm) and stringent (CHAQ-DI = 0). This analysis provides additional information on very young patients with pJIA, ages 2 to 5 years, including the full data set for the effectiveness results in this patient population, which were previously unpublished, and adds to previously published data for patients ages 6 to 17 years (10). Together with the long-term (up to 7 years) results for IV abatacept (13), the data presented here suggest that improved PROs and effectiveness outcomes are associated with abatacept treatment regardless of the formulation used and that these benefits persist over time, including in very young patients.

Persistent pain is the most common and distressing symptom of pJIA for patients, and pain reduction is a priority for both patients and parents/caregivers (32–34). Therefore, the reduction in pain score in this study, which began early in treatment, led to continued improvement, moving from moderate to mild pain in both cohorts that was maintained over time. Chronic absenteeism is commonly defined as missing 10% or more of school days (18 days/year), and in children with chronic absenteeism, up to 66% of such absences may be due to illness (35). There are

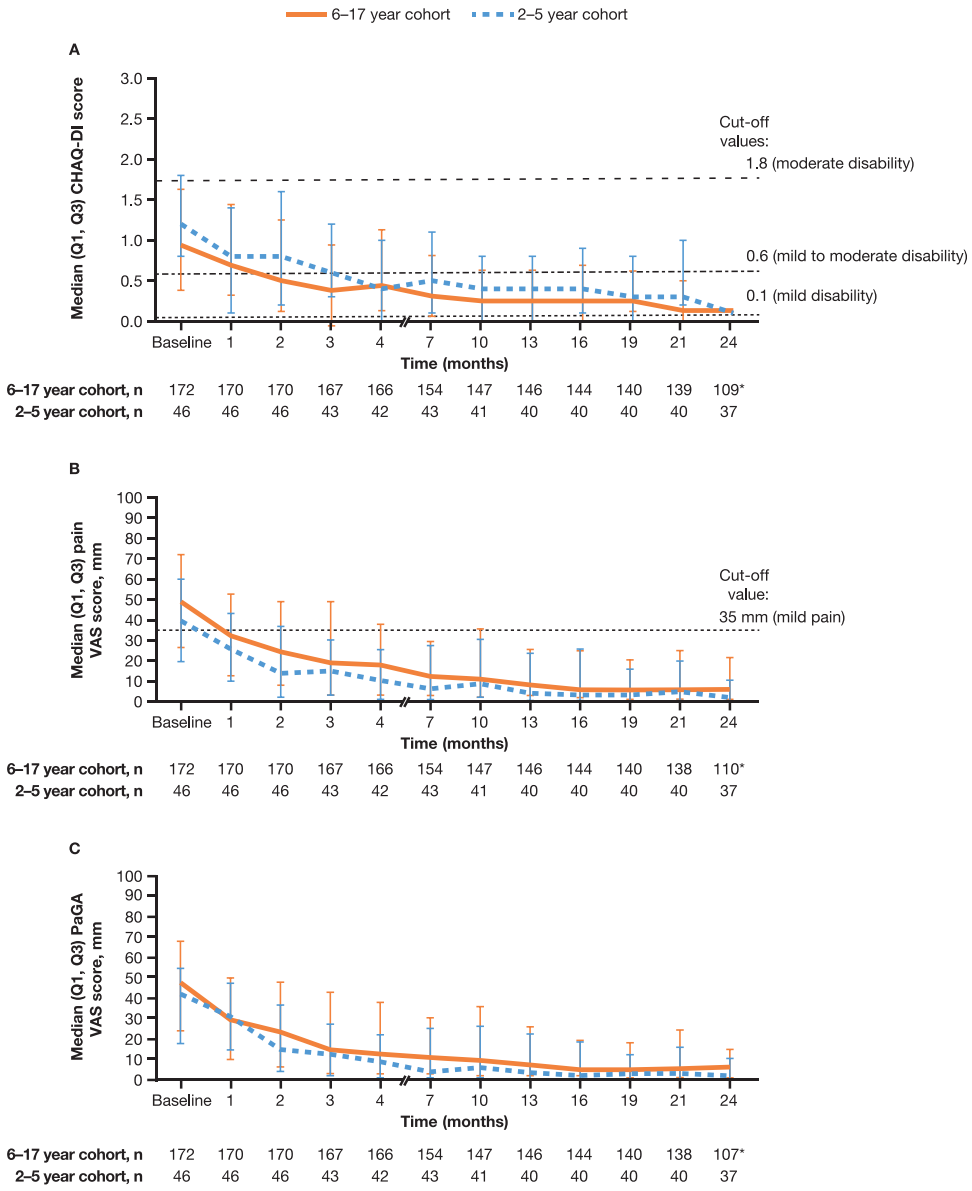


**Figure 3.** Patient-reported outcomes over time in the 6- to 17-year-old cohort and the 2- to 5-year-old cohort showing **A**, Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI); **B**, pain visual analog scale (VAS), and **C**, parent global assessment of well-being (PaGA) scores. The primary end point was measured at month 4. CHAQ-DI cutoffs: no disability = 0; mild disability = 0.1; mild to moderate disability = 0.6; moderate disability = 1.8 (21). Cutoff for mild pain = 35 mm (23). Data presented for month 24 do not accurately represent the efficacy outcomes at this time point because fewer patients in the 6- to 17-year-old cohort had data collected at this visit. n is the number of patients evaluated; error bars reprsent Q1, Q3 values; "as observed" analysis conducted.

limited studies addressing missed school days in patients with JIA; however, one study showed that chronic absenteeism was associated with high CHAQ-DI scores, disease activity, and depressive symptoms (36). Our study showed that abatacept was associated with reduced CHAQ-DI scores and disease activity as well as a decrease in the number of missed school days. Importantly, the improvements in PROs in our study not only benefited patients—with reductions in pain and increased school attendance—but also included a positive impact for caregivers, with fewer paid care days and missed workdays. In addition, patients of different ages will likely require a different extent of paid care, resulting in differences between age cohorts, with younger patients requiring more paid care than older patients.

Two studies in patients with JIA (ages 2 to 17 years) who were treated with either tocilizumab or golimumab have demonstrated improvements in PROs (CHAQ-DI, Child Health Questionnaire [CHQ]) over 16 weeks of treatment (37,38). Other studies in patients ages between 8 and 24 years have also reported improvements in PROs (CHAQ-DI, CHQ, Health Utilities Index mark 3) with both short- and long-term bDMARD treatment

**Table 2.** ALQ for the 6- to 17-year-old cohort and the 2- to 5-year-old cohort*

| Questionnaire item | Median (IQR) change from baseline | | | | | |
|---|---|---|---|---|---|---|
| | Month 2 | Month 4 | Month 10 | Month 16 | Month 21 | Month 24 |
| 6- to 17-year-old cohort† | | | | | | |
| Absolute numbers of missed school days | 0.0 (−3.0 to 0.0) | −1.0 (−3.0 to 0.0) | −0.5 (−3.0 to 0.0) | −1.0 (−3.0 to 0.0) | −1.0 (−3.0 to 0.0) | −1.0 (−3.0 to 0.0) |
| Number of paid care days | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) |
| Number of missed parent/caregiver activity days | −1.0 (−3.0 to 0.0) | −1.5 (−4.0 to 0.0) | −1.0 (−4.0 to 0.0) | −2.0 (−4.0 to 0.0) | −2.0 (−4.0 to 0.0) | −2.0 (−4.0 to 0.0) |
| 2- to 5-year-old cohort‡ | | | | | | |
| Absolute numbers of missed school days | 0.0 (−5.0 to 0.0) | 0.0 (−5.0 to 0.0) | 0.0 (−5.0 to 0.0) | −0.5 (−5.0 to 0.0) | −1.0 (−5.0 to 0.0) | −1.0 (−5.0 to 0.0) |
| Number of paid care days | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) |
| Number of missed parent/caregiver activity days | 0.0 (−3.0 to 0.0) | −1.0 (−5.0 to 0.0) | 0.0 (−5.0 to 0.0) | −0.5 (−5.0 to 0.0) | −1.0 (−7.0 to 0.0) | −1.0 (−6.5 to 0.0) |

* Data show improvement of number of days missed over time. The more likely the disease is controlled, the less likely is the need for children to miss school or for the parents to have the need for paid care, i.e., greater negative number indicates greater improvement. ALQ = Activity Limitation Questionnaire; IQR = interquartile range.
† For the 6- to 17-year-old cohort, the median (IQR) values at baseline were absolute numbers of missed school days, 2.0 (0.0–4.0); number of paid care days, 0.0 (0.0–0.0); and number of missed parent/caregiver activity days, 2.0 (0.0–5.0).
‡ For the 2- to 5-year-old cohort, the median (IQR) values at baseline were absolute numbers of missed school days, 1.0 (0.0–5.0); number of paid care days, 0.0 (0.0–0.0); and number of missed parent/caregiver activity days, 3.0 (0.0–7.0).

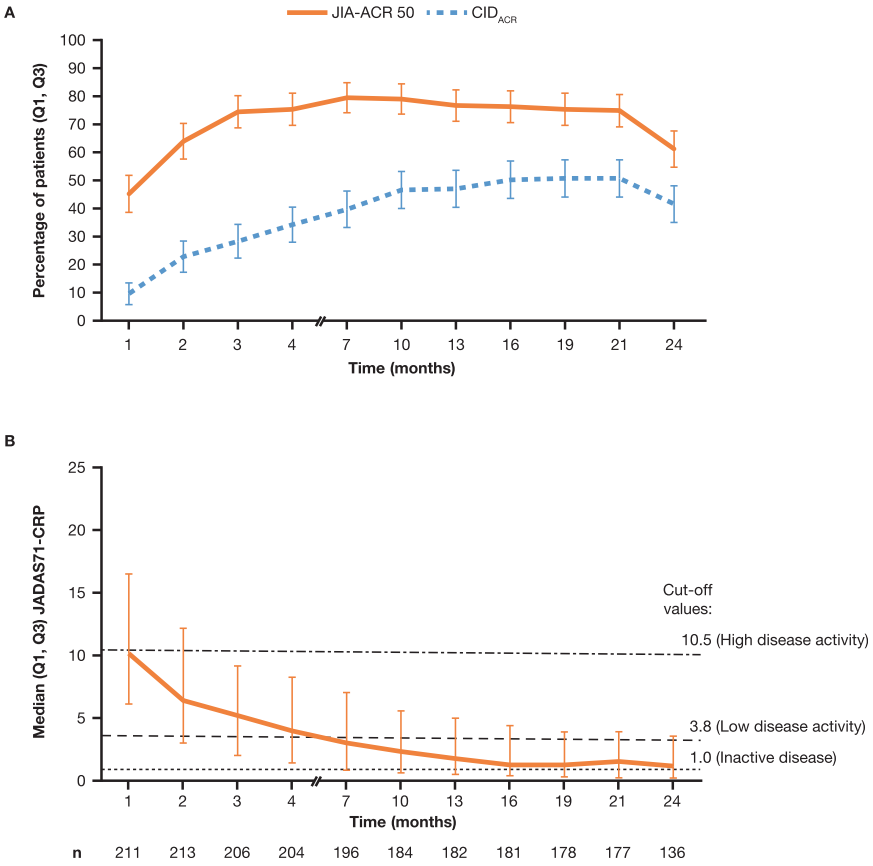


**Figure 4.** Clinical outcomes over time. **A**, Proportion of patients with ≥50% improvement in juvenile idiopathic arthritis according to the American College of Rheumatology criteria (JIA-ACR 50) and clinically inactive disease according to modified ACR critieria (CID$_{ACR}$) over time (combined data for both cohorts [patients ages 2 to 17 years; n = 219]). For missing values, a nonresponder imputation was applied, except up to month 4 if missing measurements were between 2 time points for which a response was observed. In that case, the responder was imputed. **B**, Median (Q1, Q3) Juvenile Arthritis Disease Activity Score in 71 joints using the C-reactive protein level (JADAS71-CRP) over time (combined data for both cohorts [patients ages 2–17 years; n = 219]). Dashed line represents the JADAS71-CRP cutoff value for clinically relevant low disease activity (≤3.8), the dotted line represents the JADAS71-CRP cutoff value for inactive disease (≤1), the dotted and dashed line represents the JADAS71-CRP cutoff value for high disease activity (>10.5), and n is the number of patients evaluated (30). Data presented for month 24 do not accurately represent the efficacy outcomes at this time point because fewer patients in the 6- to 17-year-old cohort had data collected at this visit. Sensitivity analysis determined no effect with exclusion of data (data not shown). Efficacy end points for the individual cohorts have been published (10).

(39–41). Two registries have reported improvements in health-related quality of life (HRQoL) in patients with JIA treated with either adalimumab plus MTX versus MTX over 1 year or with IV or SC abatacept over 5 years (42,43). Our phase III study, which includes data for 46 patients ages 2 to 5 years, builds on the limited data available on the effect of bDMARDs on quality of life in young patients with pJIA. This is particularly important because early treatment with DMARDs is associated with better disease control, clinical outcomes, and HRQoL in both children and adults (15,16). Limited information has been published on pain reduction with approved bDMARD treatment for children with JIA (14,44). A small study comparing pain experience in children with JIA treated with TNFis (n = 41) or nonbiologic standard treatment (n = 50) showed that functional disability and pain intensity were similar with both treatments, but disease activity was significantly lower with anti-TNFs (44). The phase III study of IV abatacept showed that during the 4-month open-label period, pain was reduced in abatacept-treated patients, and improvements in pain were increased further during the 6-month double-blind period (14).

Some limitations of this study were the open-label, single-arm trial design and the use of "as observed" data for some analyses. In addition, care should be taken when interpreting these results because of the smaller sample size in the 2- to 5-year-old cohort. The PRO assessments also included parent or caregiver assessments; variation can exist between physicians, patients, and their caregivers with regard to global assessments of JIA, and therefore, it is important to interpret these data in this context (45–48). Finally, there was a lack of systematic follow-up of patients who did not respond to abatacept at four months. Following standard practice for phase III trials in JIA, patient follow-up was stopped a few weeks after drug discontinuation.

The strengths of this study are that it included 46 patients ages 2 to 5 years with pJIA, which adds to the scarce body of evidence in this population. The study was conducted over 24 months, and the improvements seen in PROs and clinical outcomes were maintained throughout this time period in patients who continued treatment. The PRO data used in this study included more stringent end points than the phase III to IV abatacept trial, including CHAQ-DI = 0 and pain VAS <35 mm. In addition, the PRO data collected were broad, encompassing not only treatment impact on patients but also its impact on caregivers.

In conclusion, early and clinically meaningful improvements in both PROs and clinical outcomes were reported in patients ages 6 to 17 years and 2 to 5 years receiving SC abatacept; these improvements were sustained over 2 years.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Riddle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Ruperto, Lovell, Wong, Martini, Brunner.

**Acquisition of data.** Berman, Ávila-Zapata, Horneff, Alessio, Becker, Belot, Burgos-Vargas, Gamir, Goldenstein-Schainberg, Scheibel, Terreri, Zemel.

**Analysis and interpretation of data.** Ruperto, Lovell, Zhuo, Askelson, Wong, Martini, Brunner.

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Bristol Myers Squibb facilitated the study design, provided writing assistance for the manuscript, and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Professional medical writing and editorial assistance was provided by Claire Line, PhD, at Caudex and was funded by Bristol Myers Squibb under the guidance of PRINTO and PRCSG officers (NR, DJL, AM, and HIB). Publication of this article was not contingent upon approval by Bristol Myers Squibb.

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