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Abatacept as Monotherapy and in Combination With Methotrexate in Patients With Juvenile Idiopathic Arthritis: Analysis of 2 Phase III Trials

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ABSTRACT. ***Objective.*** To describe the efficacy and safety data of children with polyarticular-course juvenile idiopathic arthritis (pcJIA) treated with abatacept (ABA) + methotrexate (MTX) or ABA monotherapy when prior MTX use was either ineffective or not tolerated.

Methods. Posthoc analysis of 2 phase III trials of subcutaneous (SC) and intravenous (IV) ABA over 2 years in patients with pcJIA (aged 2-17 years). Patients were stratified by treatment with ABA + MTX or ABA monotherapy and further by prior biologic use. Efficacy outcomes included JIA–American College of Rheumatology (JIA-ACR) responses, Juvenile Arthritis Disease Activity Score in 27 joints using C-reactive protein (JADAS27-CRP), and safety. Descriptive pharmacokinetic analyses were also performed.

Results. Efficacy responses (JIA-ACR and JADAS27-CRP) were similar between patients receiving ABA + MTX (n = 310) or ABA monotherapy (n = 99) and persisted over 2 years. Clinical response rates were similar in biologic-naïve patients and prior biologic users; this was independent of MTX use. Across both studies, ABA + MTX and ABA monotherapy displayed similar safety profiles. Pharmacokinetic results revealed similar minimum steady-state trough ABA concentrations between studies. Further, baseline MTX did not influence ABA clearance and was not a significant predictor of JIA-ACR responses.

Conclusion. ABA monotherapy (SC and IV) was effective and well tolerated in children with pcJIA when prior MTX use was ineffective or not tolerated. Treatment effects of ABA appear to be independent of MTX coadministration. Consequently, ABA monotherapy can be considered for those with prior biologic therapy if MTX use is inappropriate. (ClinicalTrials.gov: NCT01844518 and NCT00095173)

Key Indexing Terms: biological therapy, disease-modifying antirheumatic drugs, juvenile idiopathic arthritis, methotrexate

Juvenile idiopathic arthritis (JIA) is a clinical term encompassing a heterogeneous group of conditions defined as arthritis persisting for ≥ 6 weeks, with onset in patients aged < 16 years.[1,2] Symptoms, caused by severe inflammation of the joints and subsequent damage, include pain, limitation of motion, loss of physical function, and diminished quality of life, especially with polyarticular-course JIA (pcJIA).[3]

Current American College of Rheumatology (ACR) guide-

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lines recommend that most categories of pcJIA be treated initially with methotrexate (MTX) monotherapy, the most widely used conventional synthetic disease-modifying antirheumatic drug (DMARD).[4,5] However, lack of response or poor tolerance to MTX is common among patients with pcJIA.[6-13] Common side effects of MTX include mouth sores, nausea and vomiting, cytopenia, and transaminitis.[6] If disease activity persists, or if there is intolerance to MTX, current guidelines recommend introducing a biologic agent (eg, a tumor necrosis factor inhibitor [TNFi], abatacept [ABA], or tocilizumab). MTX treatment is often continued in combination with a biologic agent. Indeed, many phase III trials of biologic agents studied these agents in combination with MTX.[4,9,13-21] However, ACR recommendations are conditional and biologic agent monotherapy seems preferable for the reason of limiting treatment side effects and cost.

ABA is a selective CD80/86 costimulation modulator that is effective and well tolerated in patients with pcJIA, both in its intravenous (IV) and subcutaneous (SC) formulation.[12,13] Initially, the use of ABA to treat patients with pcJIA was based on clinical results in adult patients with rheumatoid arthritis (RA), and was restricted to use in combination with MTX. Over time, subsequent studies and postmarketing experience have demonstrated ABA to be effective in different groups of patients with pcJIA, including as monotherapy and in biologic-naïve patients.[12,13,22,23]

Herein, we present efficacy and safety data of children with pcJIA treated with ABA monotherapy when prior MTX use was either ineffective or not tolerated, and describe the efficacy and safety of ABA when combined with MTX.

METHODS

This is a posthoc analysis of 2 phase III trials of SC and IV ABA (ClinicalTrials.gov: NCT01844518 and NCT00095173, respectively) in patients with pcJIA (oligoarticular extended, polyarthritis positive or negative for rheumatoid factor, and systemic without active systemic manifestations at time of enrollment) receiving ABA + MTX (combination therapy) or ABA monotherapy.[12,13] A schematic diagram of the 2 SC and IV ABA trials, as previously reported, is provided (Supplementary Figure S1, available with the online version of this article). Trial procedures were conducted in accordance with the Declaration of Helsinki,[24] the International Conference on Harmonization Guidelines for Good Clinical Practice, and local regulations. Patients were enrolled from 48 centers in 12 countries for the SC trial and from 43 centers in 11 countries for the phase IV trial, including the Pediatric Rheumatology International Trials Organization (PRINTO) and Pediatric Rheumatology Collaborative Study Group (PRCSG) networks.[25,26] At every study site, the protocol and amendments were reviewed and approved by the relevant independent review boards or ethics committees. All patients or their legal representatives provided written informed consent forms prior to study entry. An independent safety monitoring committee monitored adverse events (AEs) throughout the trial.

SC ABA: trial design and inclusion criteria. The SC ABA trial was a 24-month, phase III, single arm, open-label, international, multicenter, 2-part design evaluating children aged 2-17 years with active JIA (at least 2 active joints and 2 joints with a limited range of motion) who had an insufficient therapeutic response or prior intolerance to at least 1 biologic or nonbiologic DMARD.[12] Weekly SC ABA dosing was weight-tiered: 50 mg (10 to < 25 kg), 87.5 mg (25 to < 50 kg), or 125 mg (≥ 50 kg). Patients who met the JIA-ACR 30% improvement criteria (JIA-ACR30)[27] at month 4 (end of part 1) were given the option to continue SC ABA to month 24 (end of part 2; Supplementary Figure S1, available with the online version of this article). After part 2, a long-term follow-up began, in which patients who completed both parts of the study entered a poststudy drug access program.

IV ABA: trial design and inclusion criteria. The IV ABA study was a randomized, double-blind, placebo-controlled withdrawal trial evaluating children with active pcJIA aged 6 years to 17 years who had an insufficient therapeutic response or intolerance to at least 1 biologic or nonbiologic DMARD.[13] Enrolled patients received IV ABA by weight (10 mg/kg) on days 1, 15, and 29, and monthly thereafter until day 113 (end of period A). On day 113, patients who had achieved JIA-ACR30 were randomized to receive either ABA (10 mg/kg) or placebo monthly for 6 months (period B) or until a flare of arthritis. A flare was defined as a worsening of ≥ 30% in ≥ 3 of the 6 ACR core response variables for JIA, and a ≥ 30% improvement in ≤ 1 variable during the double-blind period.[28] Patients were given the option to receive open-label ABA in a 5-year follow-up treatment period (period C; Supplementary Figure S1, available with the online version of this article).

Assessments. Efficacy results for this study were measured on days 113, 393, and 645. Efficacy variables evaluated in both studies included 70%

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improvement in JIA-ACR criteria (JIA-ACR70), JIA-ACR inactive disease (ID),[27,29] and postbaseline mean (SD) Juvenile Arthritis Disease Activity Score in 27 joints using C-reactive protein (JADAS27-CRP).[30-32] JADAS27-CRP can be interpreted as follows: JADAS27-CRP low disease activity (LDA) for scores of 1.1-3.8, and JADAS27-CRP ID for scores ≤ 1.[30-32] Prespecified exploratory end points included median postbaseline values of the 6 JIA-ACR core set variables[27]: (1) number of active joints, (2) number of joints with limitation of motion, (3) physician global assessment of disease activity, (4) parental global assessment of patient overall well-being, (5) cross-culturally adapted and validated version of the Childhood Health Assessment Questionnaire–Disability Index,[33] and (6) CRP level. Improvement was defined as at least 30% improvement from baseline in 3 of any 6 variables, with no more than 1 of the remaining variables worsening by ≥ 30%.[27,29]

Serious AEs (SAEs), overall AEs, and AEs related to the study drug were recorded as per Medical Dictionary for Regulatory Activities Terminology, version 9 and 21, for the IV and SC studies, respectively. Pharmacokinetic (PK) analyses included minimum steady-state trough concentration (C_{minss}), population PK (conducted to characterize ABA serum concentration–time profiles in 2–17-year-old patients with pcJIA to determine the effects of key covariates on ABA PK variables and exposure), and exposure–response analysis. Enzyme-linked immunosorbent and electrochemiluminescence immunoassays were used to determine immunogenicity for the IV and SC studies, respectively.[34]

Statistical analyses. Descriptive analysis included calculation of median (IQR), mean (SD), or proportions, as appropriate. Safety data were exposure-adjusted and expressed as incidence rate (IR) per 100 patient-years (PY). With the exception of time to flare in the IV study, no formal statistical testing was conducted and all data are presented as intent to treat, with results separated by study. Patients randomized to the placebo group in the IV study during period B were excluded from the day 393 and 645 analyses (Supplementary Figure S1, available with the online version of this article). As a result, patients analyzed at days 393 and 645 from the IV study are those continuously treated with ABA in periods A, B, and C. Patients were stratified for both studies according to (1) MTX use (all patients), (2) prior MTX use discontinued because of lack of efficacy or intolerance, (3) prior biologic DMARD use, and (4) prior MTX and prior biologic DMARD use.

RESULTS

Baseline characteristics. Overall, 409 patients from the SC (n = 219) and IV (n = 190) studies were included in the analysis (Supplementary Figure S2, available with the online version of this article). There were 310 (75.8%) patients receiving combination therapy (172 [55.5%] in the SC study and 138 [44.5%] in the IV study) and 99 (24.2%) patients receiving ABA monotherapy (47 [47.5%] in the SC study and 52 [52.5%] in the IV study). Table 1 shows that baseline disease characteristics were generally similar between studies and between treatment groups other than some differences in pcJIA categories, disease duration, and prior DMARD exposure. The median prednisolone dose over 2 years was similar between the ABA + MTX and ABA monotherapy groups. Baseline patient characteristics and disposition by combination therapy or ABA monotherapy and reason for discontinuation are presented in Supplementary Table S1 and Supplementary Figure S3, respectively.

Clinical efficacy. Efficacy responses for JIA-ACR70, JIA-ACR ID, JADAS27-CRP LDA, and JADAS27-CRP ID over time by combination therapy or ABA monotherapy from the SC study are shown in Figures 1A and 1B. Overall, patient responses for JIA-ACR70, JIA-ACR ID, JADAS27-CRP LDA, and JADAS27-CRP ID were similar between patients receiving combination therapy or ABA monotherapy (Figures 1A,B). Likewise, postbaseline mean JADAS27-CRP values between combination therapy and ABA monotherapy groups were similar at day 113 (6.0 [SD 6.7] vs 5.3 [SD 5.9], respectively), day 393 (3.4 [SD 5.0] vs 4.2 [SD 4.5], respectively), and day 645 (3.3 [SD 5.0] vs 3.5 [SD 4.4], respectively). Stratifying by prior MTX discontinuation (because of lack of efficacy or intolerance) also yielded similar JIA improvements in both treatment groups through day 645, as per JIA-ACR70, JIA-ACR ID, and JADAS27-CRP (Figures 2A,B).

When patients were stratified by prior biologic DMARD use, patients with biologic-naïve pcJIA newly treated with ABA had an overall similar clinical response at day 645 to those who failed other biologic DMARDs prior to ABA treatment; this response was independent of concomitant MTX use (Figures 3A-D). Further, patients receiving combination therapy who were biologic-naïve generally demonstrated overall response rates similar to those with prior biologic DMARD exposure at day 645 (Supplementary Figure S4, available with the online version of this article). No statistical tests were performed to evaluate if apparent differences in efficacy between groups were significant.

Clinical efficacy outcomes from the IV study showed some difference between combination therapy and ABA monotherapy, illustrating that, over time, an overall similar proportion of patients treated with ABA monotherapy achieved JIA-ACR70 and JIA-ACR ID compared with those treated with combination therapy (Figure 1C). Patients receiving combination therapy compared with ABA monotherapy demonstrated overall similar mean postbaseline JADAS27-CRP values at day 393 (7.2 [SD 7.7] vs 4.2 [SD 7.4], respectively) and day 645 (4.1 [SD 5.2] vs 1.7 [SD 4.2], respectively) and similar values at day 113 (11.6 [SD 10.0] vs 12.0 [SD 11.2], respectively). When patients from the IV study were stratified by prior MTX discontinuation and by prior biologic use, results were more divergent than the SC study, likely because of smaller patient numbers (Figures 2C,D and Figures 3C,D, respectively, and Supplementary Figure S4, available with the online version of this article).

Time to flare during period B of the IV trial is presented in Figure 4A. The flare rate at 6 months was independent of MTX use; patients who received combination therapy (19%) or ABA monotherapy (25%) had similar flare rates as those receiving placebo (56%) and placebo + MTX (52%; Figure 4A). Time to ID up to day 729 from the IV and SC trial is shown in Figures 4B and 4C. Kaplan-Meier estimates of time to ID up to day 729 of MTX treatment showed overlap between the combination therapy and ABA monotherapy curves.

Safety. A summary of AEs, infections and infestations, and gastrointestinal (GI) disorders is presented in Table 2. In the SC study, exposure-adjusted IRs per 100 PY between combination therapy and ABA monotherapy were similar for SAEs (5.1 vs 7.3, respectively), overall AEs (350.5 vs 251.5, respectively), and AEs related to study drug (79.3 vs 61.1, respectively). Infections and infestations were similar overall between combination therapy and ABA monotherapy (144.0 vs 108.7, respectively). The frequency and percentage of infections and infestations

Table 1. Baseline demographics and disease characteristics by MTX use for all treated patients.

	SC Cohort[a]		IV Cohort	
	ABA + MTX, n = 172	ABA, n = 47	ABA + MTX, n = 138	ABA, n = 52
Age at enrollment, yrs	11.0 (7.0-14.0)	11.0 (7.0-15.0)	12.0 (10.0-14.0)	13.0 (11.5-15.0)
Duration of JIA, yrs	1.0 (0.0-3.0)	2.0 (0.0-5.0)	3.0 (1.0-6.0)	5.0 (2.0-9.0)
JIA categories, n (%)				
Polyarticular RF−	97 (56.4)	26 (55.3)	55 (39.9)	29 (55.8)
Polyarticular RF+	38 (22.1)	10 (21.3)	34 (24.6)	4 (7.7)
Oligoarticular	24 (14)	9 (19.1)	17 (12.3)	13 (25)
Systemic	5 (2.9)	0 (0)	31 (22.5)	6 (11.5)
Other	8 (4.7)	2 (4.3)	0 (0)	0 (0)
PGA, 0-100 mm VAS[b]	49.3 (35.0-64.2)	44.0 (25.8-67.0)	50.5 (38.0-65.0)	58.5 (43.0-72.5)
Parent global assessment of patient overall well-being, 0-100 mm VAS[b]	47.8 (21.8-66.3)[c]	40.0 (20.0-56.8)	47.0 (28.0-59.0)	45.0 (15.5-68.5)
CHAQ-DI	1.0 (0.5-1.6)[c]	0.9 (0.4-1.5)	1.3 (0.8-1.9)	1.1 (0.5-1.7)
Active joints	10.0 (6.0-18.0)	7.0 (4.0-11.0)	12.5 (6.0-25.0)	11.0 (6.0-19.0)
Joints with LOM	8.5 (5.0-15.0)	7.0 (2.0-10.0)	12.5 (6.0-26.0)	10.5 (5.0-16.0)
CRP, mg/dL	0.3 (0.1-1.0)	0.1 (0.1-0.8)	1.4 (0.2-5.8)	1.1 (0.3-2.8)[d]
JADAS27-CRP	18.8 (13.2-25.0)[c]	14.2 (10.0-23.7)[e]	21.7 (15.5-31.1)	19.7 (15.9-27.1)
Pain VAS < 35 mm, n (%)	63 (36.6)[c]	13 (27.7)	50 (36.2)	16 (30.8)
Prior biologic use, n (%)	32 (18.6)	24 (51.1)	30 (21.7)	27 (51.9)
MTX dose, mg/kg/wk	0.4 (0.3-0.5)	NA	0.4 (0.3-0.6)	NA
Prednisone equivalent dose, mg/kg/day	0.15 (0.1-0.2)[f]	0.15 (0.1-0.2)[g]	0.14 (0.1-0.2)[h]	0.17 (0.1-0.2)[i]

Data are presented as median (IQR) unless otherwise noted. [a] Data presented reflect the cohort aged 2-17 years. [b] A score of 0 corresponds with "very well" and "inactive disease" for parent global assessment of patient overall well-being and PGA, respectively. [c] n = 171. [d] n = 51. [e] n = 46. [f] n = 54. [g] n = 6. [h] n = 71. [i] n = 17. ABA: abatacept; CHAQ-DI: Childhood Health Assessment Questionnaire–Disability Index; CRP: C-reactive protein; IV: intravenous; JADAS27-CRP: Juvenile Arthritis Disease Activity Score in 27 joints using CRP; JIA: juvenile idiopathic arthritis; LOM: limitation of motion; MTX: methotrexate; NA: not applicable; PGA: physician global assessment; RF: rheumatoid factor; SC: subcutaneous; VAS: visual analog scale.

by severity for combination therapy vs monotherapy were as follows: 109 (89%) vs 32 (91%) for mild; 43 (83%) vs 14 (93%) for moderate; and 2 (100%) vs 0 (0%) for severe, respectively. GI disorders had similar IRs per 100 PY between combination therapy and ABA monotherapy (47.9 vs 36.6, respectively). The frequency and percentage of GI disorders by severity were 57 (47%) vs 15 (43%) for mild and 14 (27%) vs 3 (20%) for moderate for combination therapy and ABA monotherapy, respectively. No severe GI disorders were reported. The SC trial had identical event counts (n = 2) and IRs per 100 PY (0.7) for hepatobiliary disorders and hepatic enzyme increases, all of which occurred in the combination therapy arm. Additional details of the SC trial separated by age and therapy can be found in Supplementary Table S2 (available with the online version of this article).

Overall, similar results were shown for the IV study (Table 2). Combination therapy and ABA monotherapy displayed similar exposure-adjusted IRs per 100 PY for SAEs (7.3 vs 10.5, respectively), overall AEs (527.0 vs 497.4, respectively), and AEs related to study drug (138.0 vs 99.5, respectively). Treatment arms displayed nearly identical rates for infections and infestations (177.4 vs 175.4, respectively). However, no statistical tests were performed to evaluate significance of differences in safety between groups. The frequency and percentage of infections and infestations by severity were 60 (82%) vs 14 (78%) for mild, 31 (72%) vs 8 (73%) for moderate, and 4 (67%) vs 1 (100%) for severe, for combination therapy and ABA monotherapy, respectively. GI disorders were more common in those treated with combination therapy compared with ABA monotherapy (IRs per 100 PY: 100.7 vs 52.4, respectively). The frequency and percentage of GI disorders by severity were 48 (66%) vs 10 (56%) for mild, 18 (42%) vs 3 (27%) for moderate, and 2 (33%) vs 0 (0%) for severe, for combination therapy and ABA monotherapy, respectively. There were no hepatobiliary disorders or hepatic enzyme increases reported for the IV trial.

ABA C_{minss} and exposure response. At day 113, ABA C_{minss} values were similar in both studies for patients treated with combination therapy or ABA monotherapy (Supplementary Table S3, available with the online version of this article). In the SC study, over 99% of all patients achieved and maintained ABA C_{minss} values near those required for maximal efficacy for ABA (≥ 10 μg/mL).[35,36] A population PK analysis (based on a previous model) showed that baseline concomitant MTX use was not a statistically significant covariate on the clearance of ABA (data not shown).

Immunogenicity. Although the different methodologies used to measure immunogenicity in the 2 studies preclude combining the data, there was a low overall incidence of antidrug antibodies in both studies.[34] Although antidrug antibodies were numerically low for the combination therapy group, they were absent in patients receiving ABA monotherapy. Immunogenicity was measured on day 729 in the SC study: combination therapy (n = 9/172 [5.2%]) vs ABA monotherapy (n = 0/172 [0%]). For

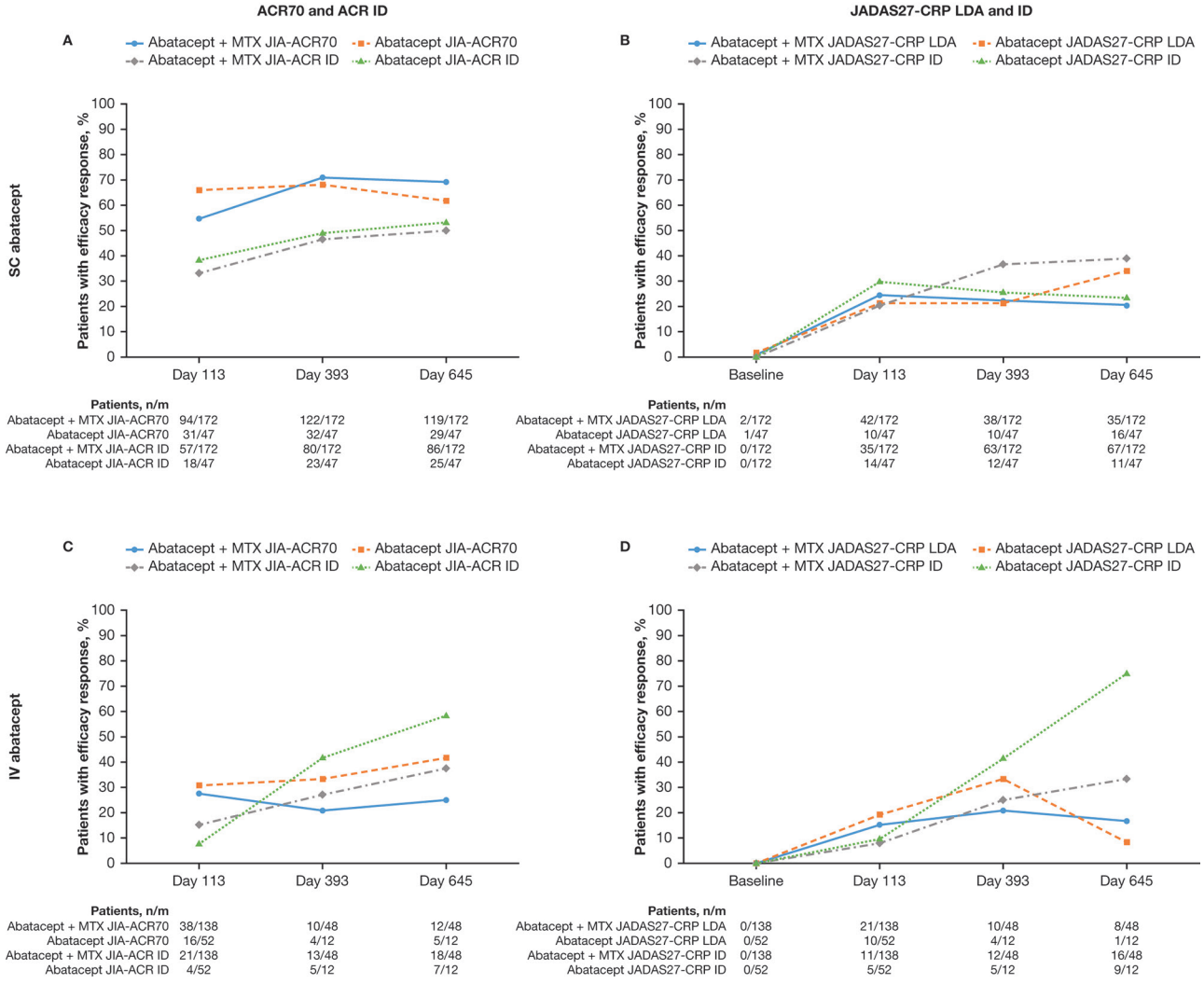

Figure 1. Efficacy responses over time[a] for all treated patients by MTX use for the SC study[b] (A and B) and IV study[c] (C and D). JADAS27-CRP LDA corresponds to scores of 1.1-3.8, and JADAS27-CRP ID to scores ≤ 1. [a] The number of patients representing each group in the analysis decreased over time. [b] Includes all treated patients. [c] Includes all patients randomized to abatacept during period B. ID: inactive disease; IV: intravenous; JADAS27-CRP: Juvenile Arthritis Disease Activity Score in 27 joints using C-reactive protein; JIA-ACR70: 70% improvement in Juvenile Idiopathic Arthritis-American College of Rheumatology criteria; LDA: low disease activity; MTX: methotrexate; n/m: number of patients with efficacy response/number of patients in the analysis; SC: subcutaneous.

the IV study, immunogenicity measures did not include patients randomized to receive placebo during period B (Supplementary Figure S1, available with the online version of this article). Immunogenicity was measured in periods A and B in the IV study: combination therapy (n = 8/92 [9%]) vs ABA monotherapy (n = 0/36 [0%]).

DISCUSSION

This posthoc analysis of 2 phase III trials evaluated efficacy and safety of ABA + MTX combination therapy or ABA monotherapy in patients with pcJIA. The monotherapy arms had efficacy responses comparable to those of patients receiving combination therapy, despite the small number of patients in these groups (ABA was given when prior MTX was discontinued because of lack of efficacy or intolerance). This was observed with both SC and IV ABA administration in children aged 2 years to 17 years with pcJIA. These results were consistent across a range of pcJIA response measures and sustained for approximately 2 years. In the SC study, responses between the combination therapy and ABA monotherapy groups remained comparable in efficacy between subgroups of patients receiving ABA monotherapy in whom MTX was inappropriate because of lack of efficacy or intolerance. Responses between combination therapy and ABA monotherapy in the IV study subgroup analyses were less consistent, most likely because of small sample sizes.

Clinical response rates were similar or numerically higher in patients with pcJIA who did not receive prior biologic therapy than in those who had failed prior biologic therapy. This finding was not unexpected; in general, patients who are resis-

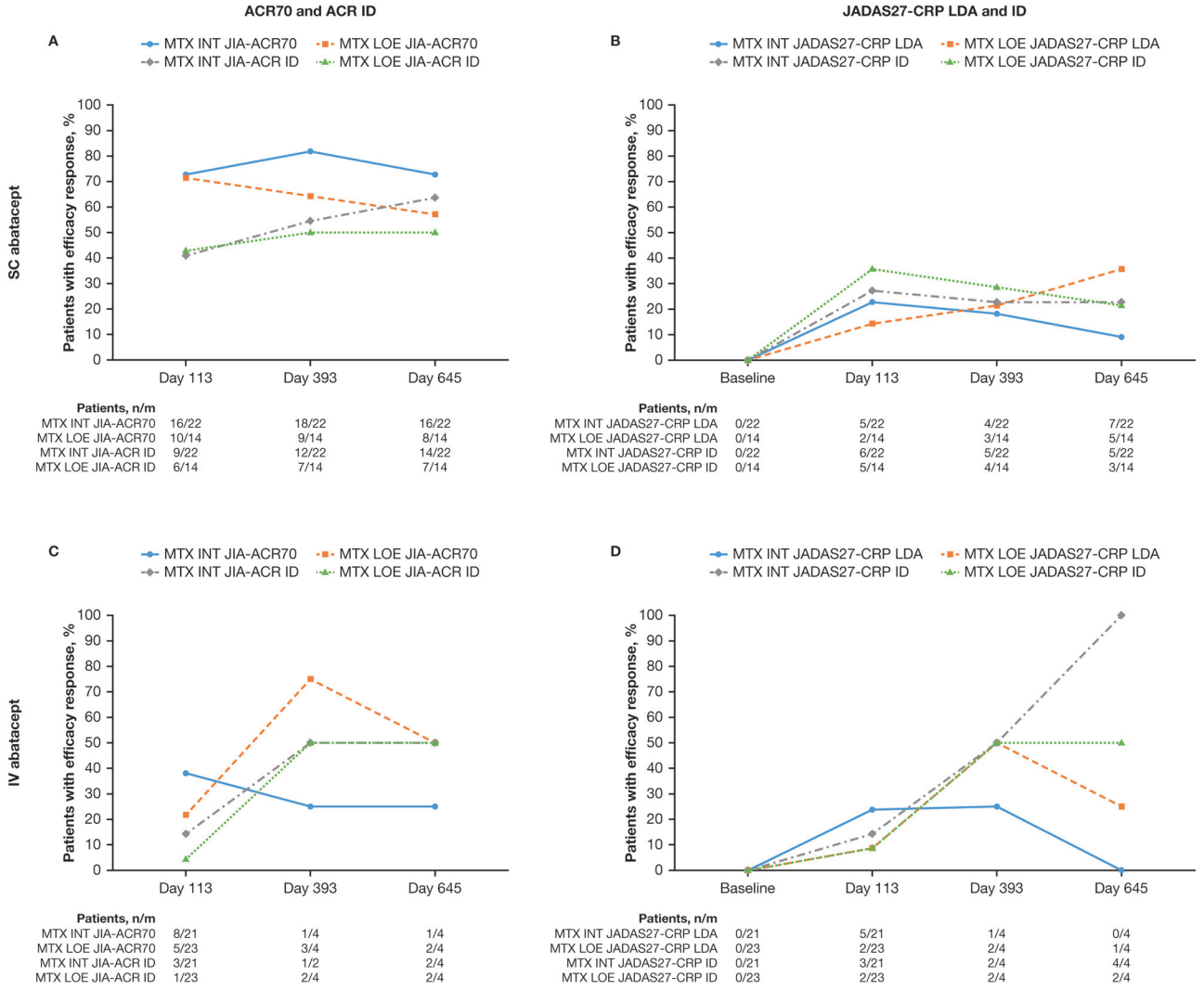

Figure 2. Efficacy responses over time[a] by MTX discontinuation within the SC study[b] (A and B) and the IV study[c] (C and D) because of lack of efficacy or intolerance[d]. JADAS27-CRP LDA: 1.1-3.8; JADAS27-CRP ID: ≤ 1. [a] The number of patients representing each group in the analysis decreased over time. [b] Includes all treated patients. [c] Includes all patients randomized to abatacept during period B. [d] All panels display patients receiving abatacept monotherapy because of MTX discontinuation from either lack of efficacy (MTX LOE) or intolerance (MTX INT). ID: inactive disease; INT: intolerance; IV: intravenous; JADAS27-CRP: Juvenile Arthritis Disease Activity Score in 27 joints using C-reactive protein; JIA-ACR70: 70% improvement in Juvenile Idiopathic Arthritis-American College of Rheumatology criteria; LDA: low disease activity; LOE: loss of efficacy; MTX: methotrexate; n/m: number of patients with efficacy response/number of patients in the analysis; SC: subcutaneous.

tant to TNFi therapy have a lower rate of response to a second biologic.[37] Biologic-naïve patients should have a higher rate of response to ABA compared with those who received prior TNFi therapy, and those without prior biologic use presumably represent patients with early disease who are likely to respond better. Lending support to this hypothesis, no discernible differences could be identified for time to flare or time to ID between therapy arms. However, further research is needed to bolster this assertion; said research may help identify target candidates likely to respond to biologic DMARD treatment.

In both the IV and SC studies, the rates (assessed using IR/100 PY) of overall AEs and AEs related to study drug were higher with combination therapy vs ABA monotherapy, as expected. The rates of GI AEs, however, were actually lower with combination therapy in the 2- to 5-year-old cohort. Therefore, the higher rate of overall AEs with combination therapy in the SC study may have been driven by higher rates of infections and infestations in the 2- to 5-year-old cohort.

On day 113, no clinically meaningful imbalance in ABA C_{minss} (> 10 μg/mL) was identified. The absence of imbalance in C_{minss} blood levels minimizes the potential for a more favorable efficacy response for either therapy. As a result, ABA C_{minss} blood levels were therefore adequate in assessing the efficacy of SC and IV ABA with or without MTX. The population PK analysis, which was based on a model that included data from adult RA studies,[35] as well as JIA studies,[36] showed that baseline concomitant MTX was not a statistically significant covariate affecting the clearance of ABA. Exposure–response analysis from both studies also demonstrated that MTX was not a significant covariate and does not affect the prediction of JIA-ACR response in patients

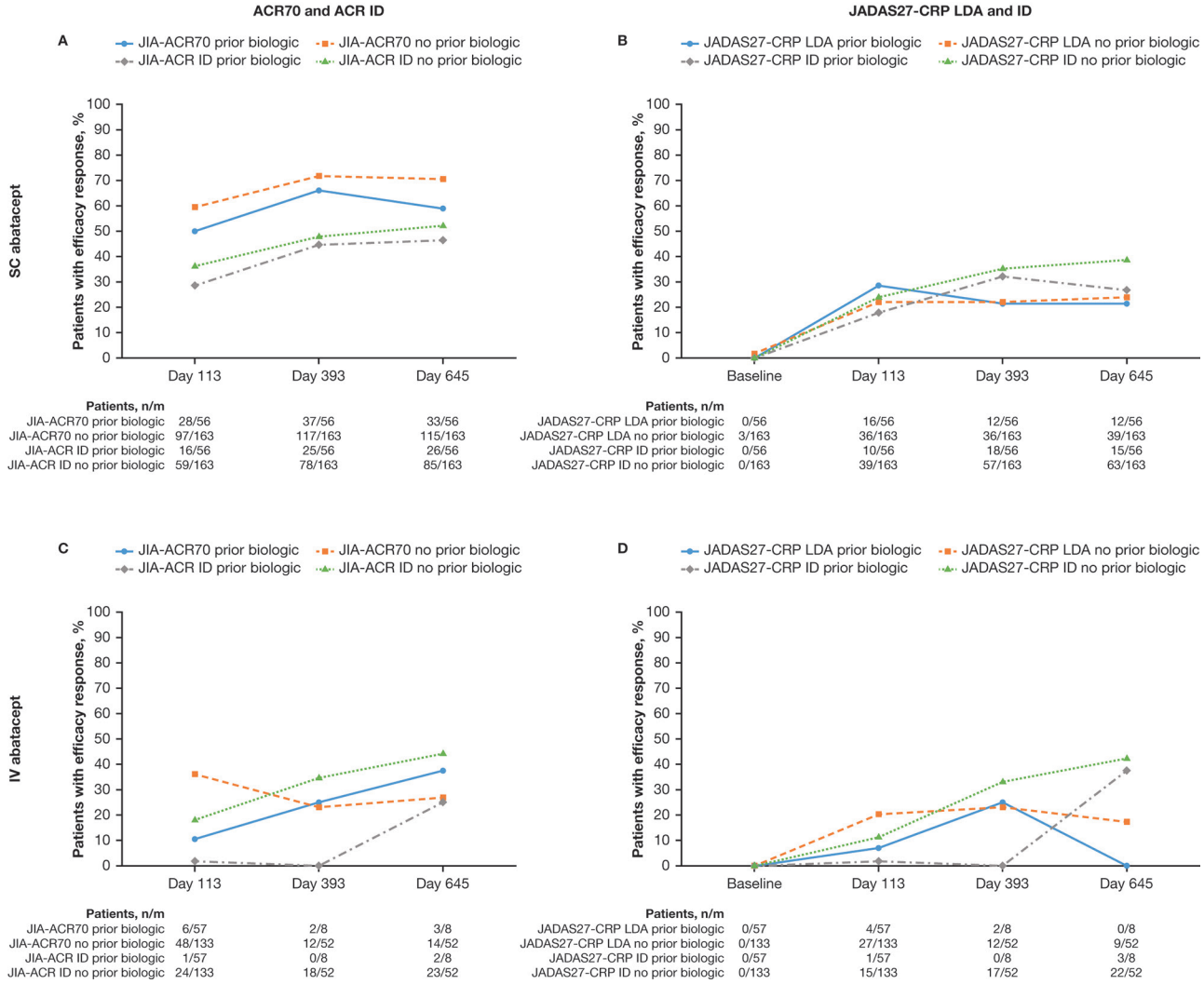

Figure 3. Efficacy responses over time[a] by prior biologic use within the SC study[b] (A and B) and the IV study[c] (C and D). JADAS27-CRP LDA: 1.1-3.8; JADAS27-CRP ID: ≤ 1. [a] The number of patients representing each group in the analysis decreased over time. [b] Includes all treated patients. [c] Includes all patients randomized to abatacept during period B. ID: inactive disease; IV: intravenous; JADAS27-CRP: Juvenile Arthritis Disease Activity Score in 27 joints using C-reactive protein; JIA-ACR70: 70% improvement in Juvenile Idiopathic Arthritis-American College of Rheumatology criteria; LDA: low disease activity; n/m: number of patients with efficacy response/number of patients in the analysis; SC: subcutaneous.

with pcJIA. Overall, the incidence of antidrug antibodies was low in patients receiving ABA with and without MTX; there was no measurable clinical effect in patients who were antidrug antibody–positive in either study.

Study strengths include a large overall sample size, and efficacy and safety results that were consistent across pcJIA response measures for both the SC and IV formulations of ABA that persisted for approximately 2 years. The major limitation of this study was the small patient numbers in subgroups, including the subgroup receiving IV ABA who had been treated with prior biologics; therefore, a comparative analysis with significance testing was not performed.

In summary, combination therapy or ABA monotherapy (SC and IV) were effective and well tolerated in children with pcJIA when prior MTX use was either ineffective or not tolerated. Clinical response rates were similar or greater among biologic-naïve patients, which was independent of MTX use. These results support the use of SC or IV ABA in children with pcJIA, both in combination with MTX or as monotherapy for patients with prior biologic therapy for whom MTX use is inappropriate.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

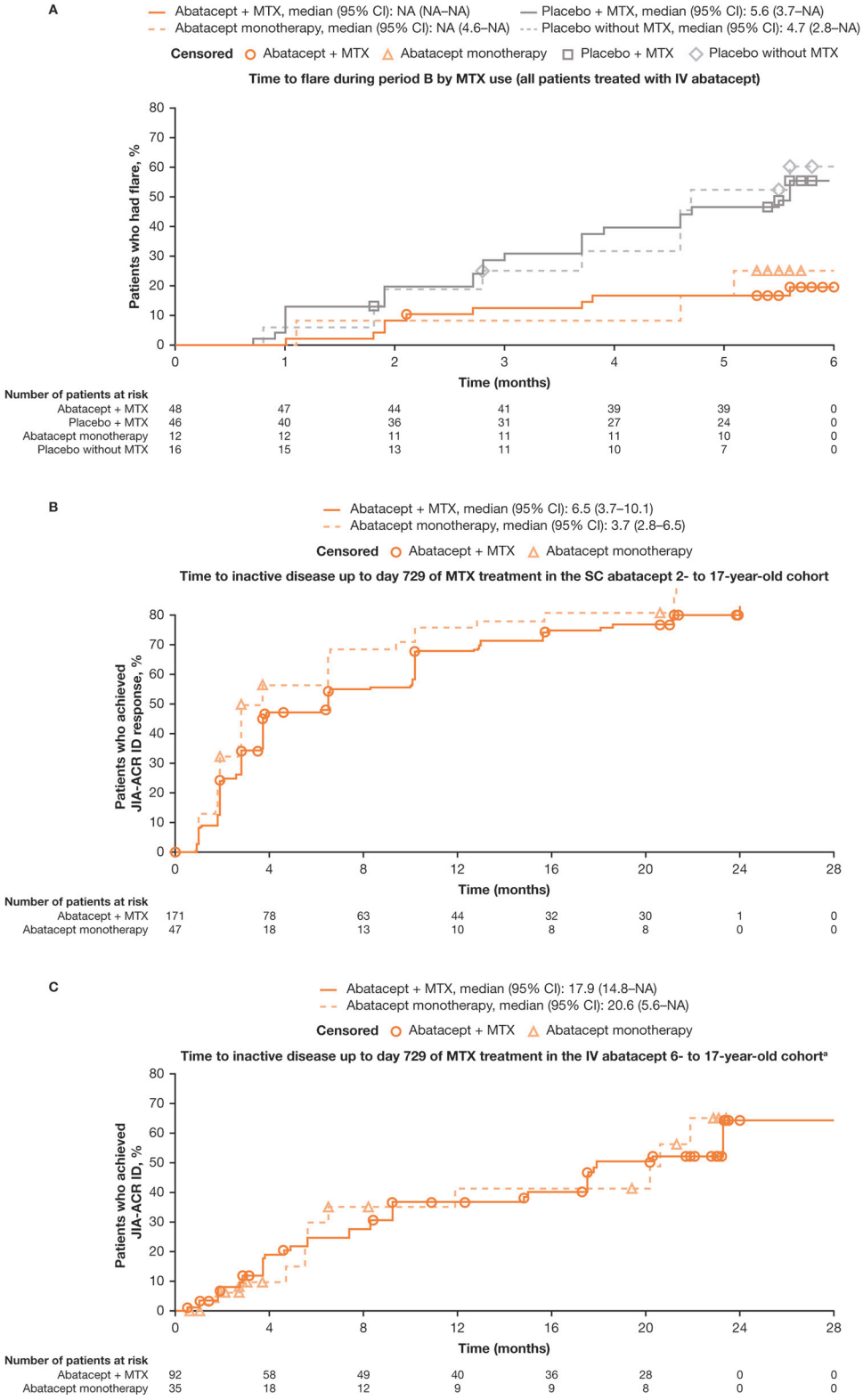

Figure 4. Kaplan-Meier estimates of (A) time to flare or (B,C) inactive disease. [a] All treated patients excluding those randomized to placebo in period B. ACR: American College of Rheumatology; ID: inactive disease; IV: intravenous; JIA: juvenile idiopathic arthritis; MTX: methotrexate; NA: not applicable; SC: subcutaneous.

Table 2. Summary of exposure-adjusted adverse events by MTX use[a].

	SC Cohort		IV Cohort	
	ABA + MTX, n = 172	ABA, n = 47	ABA + MTX, n = 92	ABA, n = 36
SAEs	15 (5.1)	6 (7.3)	10 (7.3)	4 (10.5)
Overall AEs	1025 (350.5)	206 (251.5)	722 (527.0)	190 (497.4)
AEs related to study drug	232 (79.3)	50 (61.1)	189 (138.0)	38 (99.5)
AEs of special interest				
Malignancy	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Autoimmune disease	3 (1.0)	0 (0.0)	0 (0.0)	4 (10.5)
Infections and infestations	421 (144.0)	89 (108.7)	243 (177.4)	67 (175.4)
Acute tonsilitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.9)
Bronchitis	9 (3.1)	3 (3.7)	5 (3.6)	2 (5.2)
Cellulitis	0 (0.0)	1 (1.2)	1 (0.7)	0 (0.0)
Ear infection	4 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)
Enterobiasis	1 (0.3)	1 (1.2)	1 (0.7)	0 (0.0)
Gastroenteritis	17 (5.8)	6 (7.3)	12 (8.8)	0 (0.0)
Impetigo	3 (1.0)	0 (0.0)	4 (2.9)	0 (0.0)
Influenza	17 (5.8)	5 (6.1)	23 (16.8)	4 (10.5)
Laryngitis	0 (0.0)	2 (2.4)	0 (0.0)	2 (5.2)
Nasopharyngitis	104 (35.6)	23 (28.1)	26 (19.0)	5 (13.1)
Otitis media	2 (0.7)	2 (2.4)	2 (1.5)	0 (0.0)
Pharyngitis	19 (6.5)	1 (1.2)	10 (7.3)	2 (5.2)
Rhinitis	28 (9.6)	5 (6.1)	15 (10.9)	3 (7.9)
Scarlet fever	2 (0.7)	1 (1.2)	0 (0.0)	0 (0.0)
Sinusitis	11 (3.8)	3 (3.7)	19 (3.9)	1 (2.6)
Tonsilitis	13 (4.4)	2 (2.4)	8 (5.8)	8 (20.9)
Tracheitis	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	66 (22.6)	11 (13.4)	32 (23.4)	13 (34.0)
Urinary tract infection	11 (3.8)	3 (3.7)	7 (5.1)	6 (15.7)
Varicella	3 (1.0)	0 (0.0)	2 (1.5)	1 (2.6)
Viral infection	0 (0.0)	1 (1.2)	1 (0.7)	2 (5.2)
GI disorders	140 (47.9)	30 (36.6)	138 (100.7)	20 (52.4)
Abdominal pain	15 (5.1)	6 (7.3)	12 (8.8)	4 (10.5)
Aphthous ulcer	9 (3.1)	1 (1.2)	0 (0.0)	0 (0.0)
Mouth ulceration	0 (0.0)	3 (3.7)	16 (11.7)	0 (0.0)
Nausea	32 (10.9)	3 (3.7)	25 (18.2)	2 (5.2)
Vomiting	23 (7.9)	4 (4.9)	15 (10.9)	4 (10.5)
Hepatobiliary disorders	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic enzyme increases	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)

All values shown as n (IR/100 PY). [a] All treated patients from both studies, excluding those randomized to placebo in period B for the IV study. ABA: abatacept; AE: adverse event; GI: gastrointestinal; IR: incidence rate; IV: intravenous; MTX: methotrexate; PY: patient-years; SAE: serious adverse event; SC: subcutaneous.

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