Safety of Adalimumab in Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, Psoriasis, and Crohn's Disease

Gerd Horneff, MD[1], Marieke M. B. Seyger, MD, PhD[2], Dilek Arikan, MD[3], Jasmina Kalabic, MD[4], Jaclyn K. Anderson, DO, MS[3], Andreas Lazar, MD[4], David A. Williams, MD, MPH[3], Chen Wang, PhD[3,*], Rita Tarzynski-Potempa, MD[3], and Jeffrey S. Hyams, MD[5]

Objective To evaluate the safety of adalimumab in pediatric patients who participated in clinical trials of juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and pediatric enthesitis-related arthritis), psoriasis, and Crohn's disease.

Study design This analysis included data from 7 global, randomized, and open-label AbbVie-sponsored clinical trials of adalimumab and their open-label extensions conducted between September 2002 and December 31, 2015 (cutoff date for ongoing studies). Patients who received ≥1 dose of adalimumab subcutaneously were included. Adverse events that occurred after the first dose of adalimumab and up to 70 days (5 half-lives) after the last dose were reported and events per 100 patient-years were calculated.

Results The analysis included 577 pediatric patients, representing 1440.7 patient-years of adalimumab exposure. Across indications, the most commonly reported adverse events (events/100 patient-years) were upper respiratory tract infections (24.3), nasopharyngitis (17.3), and headache (19.9). Serious infections (4.0 events/100 patient-years) were the most frequent serious adverse events across indications; the most commonly reported was pneumonia (0.6 events/100 patient-years). Serious infection rates were 2.7, 0.8, and 6.6 events/100 patient-years in patients with juvenile idiopathic arthritis, psoriasis, and Crohn's disease, respectively. No events of malignancies were reported. One death (accidental fall) occurred in a patient with psoriasis.

Conclusions The safety profile of adalimumab in pediatric patients with polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, psoriasis, and Crohn's disease was generally similar across indications; no new safety signals were identified in the treatment of pediatric patients with adalimumab. *(J Pediatr 2018;201:166-75).*

Trial registration Clinicaltrials.gov: NCT00048542, NCT00775437, NCT00690573, NCT01166282, NCT01251614, NCT00409682, and NCT00686374.

Adalimumab is an anti–tumor necrosis factor (TNF) monoclonal antibody that has demonstrated safety and efficacy in multiple pediatric conditions, including polyarticular juvenile idiopathic arthritis (pJIA),[1-3] enthesitis-related arthritis (ERA),[4] pediatric psoriasis,[5] and pediatric Crohn's disease (CD).[6,7] Currently, the approved pediatric indications for adalimumab in the US and European Union include moderately to severely active pJIA in patients ≥2 years of age and moderate to severely active pediatric CD in patients ≥6 years of age with previous inadequate response to conventional therapy.[8] Additional approved indications for adalimumab in the European Union include the treatment of active ERA in patients ≥6 years of age with an inadequate response to or intolerance of conventional therapy and the treatment of severe chronic plaque

AE	Adverse event
CD	Crohn's disease
CHF	Congestive heart failure
ERA	Enthesitis-related arthritis
JIA	Juvenile idiopathic arthritis
NCT	National Clinical Trial
pJIA	Polyarticular juvenile idiopathic arthritis
PY	Patient-year
SAE	Serious adverse event
TB	Tuberculosis
TNF	Tumor necrosis factor

From the [1]Centre of Paediatric Rheumatology, Department of General Paediatrics, Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany; [2]Department of Dermatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; [3]AbbVie Inc., North Chicago, IL; [4]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany; and [5]Division of Digestive Diseases, Hepatology, and Nutrition, Connecticut Children's Medical Center, Hartford, CT

*Affiliation at the time of the study.

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psoriasis in children and adolescents ≥4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.[9]

The safety of adalimumab, especially long term, is an important consideration in the pediatric population, as each indication represents a distinct chronic condition. An analysis of adverse event (AE) data across multiple indications from 23 458 patients (mostly adults), some of whom had clinical trial exposure to adalimumab for almost 12 years, found that although rates of specific AEs varied by disease, the overall safety profile was consistent with that of anti-TNF agents as a class[10]; no new safety signals were identified. Although interim data from ongoing pediatric registries for pJIA, CD, and psoriasis are emerging,[11-15] pediatric safety data for adalimumab remain limited relative to adult safety data. Therefore, examining safety data within and across multiple therapeutic areas specifically in pediatric populations from controlled clinical trials may provide additional, valuable safety information. Safety events of special interest in the pediatric population include infections (particularly serious infections and opportunistic infections), malignancies, and hypersensitivity.

This analysis was conducted to evaluate the totality of safety findings from pediatric studies of adalimumab, including long-term analyses (>52 weeks), by assessing AEs in pediatric patients who participated in clinical trials of juvenile idiopathic arthritis (JIA; pJIA and ERA), psoriasis, and CD. Data from these studies reflect the longest clinical study exposure to adalimumab published to date for each indication.[1-7]

Methods

Clinical Trials

Safety findings from 7 AbbVie-sponsored, global clinical trials of adalimumab (subcutaneous injection; 40 mg/0.8-mL or 20 mg/0.4-mL formulation) in pediatric patients were included in this analysis: 4 studies of rheumatic disease, including pJIA (National Clinical Trial [NCT] no. 00048542, NCT00775437, NCT00690573) and ERA (NCT01166282); 1 study of pediatric psoriasis (NCT01251614); and 1 study of pediatric CD (NCT00409682), including its ongoing open-label extension (NCT00686374). Methods and results from these studies are published (briefly summarized in **Table I**)[1-7] All study protocols were approved by an institutional review board or independent ethics committee, and written informed consent was obtained from patients, parents, or legal guardians.

Safety Assessments

This analysis included all AEs that occurred after the first dose of adalimumab and up to 70 days (5 half-lives) after the last dose (ie, all treatment-emergent AEs); data are presented through December 31, 2015. An analysis of infections by concomitant corticosteroid use also was conducted. AEs were coded using the *Medical Dictionary for Regulatory Activities*, version 18.1. AEs of special interest included infections and serious infections, opportunistic infections (due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens),[16] malignancies, and hypersensitivity reactions. Serious adverse events (SAEs) were defined as events that were fatal or immediately life-threatening; required inpatient or prolonged hospitalization; resulted in persistent or significant disability/incapacity, congenital anomaly, or spontaneous or elective abortion; or required medical or surgical intervention to prevent a serious outcome.

Growth/height analyses were performed in 2 patient populations. In the pJIA study,[3] patients were pooled and divided into 2 groups based on their baseline height percentile (<33 or >33) on the Centers for Disease Control and Prevention growth chart.[17] Height and body mass index and improvement of pJIA signs and symptoms were evaluated. In the CD study,[6] height velocity z scores based on bone age were calculated using reference standard height velocity tables according to the following equation: (observed height velocity – median height velocity for age and sex)/SD of the median. Patients with height velocity z score ≤–1.0 were considered to have growth delay at baseline.[18] Change from baseline in height velocity z score was evaluated in patients with and without growth delay at baseline.

Statistical Analyses

Patients who received ≥1 dose of adalimumab were included in this pediatric safety analysis. AEs are presented as the number and proportion of patients experiencing each event and as the number of events and rate of events per 100 patient-years (PY). A Kaplan–Meier analysis was used to evaluate the time to first serious infectious event for each indication. Height and growth analyses were reported as observed data. For the CD growth analyses, the Wilcoxon rank sum test was used to compare change from baseline (2-sided, 5% level of significance).

Results

Baseline Characteristics and Adalimumab Exposure

This analysis included 577 pediatric patients (**Figure 1**; available at www.jpeds.com), representing 1440.7 PY of exposure (**Table II**). A total of 274 patients with JIA (806.9 PY), including 228 patients representing 662.3 PY in 3 pJIA studies and 46 patients representing 144.5 PY in the pediatric ERA study, 111 patients with pediatric psoriasis (121.5 PY), and 192 patients with pediatric CD (512.3 PY), were included in the analysis. Baseline characteristics for these pediatric populations are summarized in **Table II**.

AEs

Most patients in each therapeutic area reported at least 1 AE (**Table III**). The most common types of AEs (including both serious and nonserious events) were infections and injection-site reactions, including injection-site pain. Overall, infections occurred in 82% of patients with JIA (150.7 events/100 PY), 74% of patients with psoriasis (168.7 events/100 PY), and 76% of patients with CD (132.0 events/100 PY). Across all pediatric indications, the most commonly reported individual AEs were upper respiratory tract infections (27%; 24.3 events/100 PY), nasopharyngitis (24%; 17.3 events/100 PY), and

Table I. Overview of pediatric studies included in the current safety analysis

Authors; Clinicaltrials.gov identifiers	Year	Disease	Age range, y	No.	Study design (sites); dosing regimen
Lovell et al[3]; NCT00048542	2008	pJIA	4-17	171	Randomized, double-blind, placebo-controlled, stratified, parallel-group, multicenter study (Belgium, Czech Republic, France, Germany, Italy, Slovakia, Spain, and the US) conducted between September 2002 and January 2005 16-wk, open-label lead-in, followed by 32-wk, double-blind treatment: 24 mg/m^2 BSA adalimumab up to a maximum of 40 mg EOW Open-label extension phase: dose initially based on BSA, followed by a fixed dose based on body weight (20 mg if <30 kg; 40 mg if ≥30 kg)
Kingsbury et al[1]; NCT00775437	2014	pJIA	2 to <4*	32	Open-label, single-arm, multicenter study (Czech Republic, France, Germany, and the US) conducted between March 2009 and March 2013 24 mg/m^2 BSA (up to maximum 20 mg) adalimumab EOW for ≥24 wk
Imagawa et al[2]; NCT00690573	2012	pJIA	4-17	25	Open-label, single-arm, multicenter study (Japan) conducted between May 2008 and August 2010 20 mg adalimumab EOW if <30 kg or 40 mg adalimumab EOW if ≥30 kg up to wk 16 (dose redetermined by body weight at wk 16 and every 12 wk after wk 24 through wk 60)
Burgos-Vargas et al[4]; NCT01166282	2015	Pediatric ERA	≥6 to <18	46	12-wk, double-blind, placebo-controlled, multicenter study with an early escape option, followed by an open-label adalimumab EOW treatment period with a maximum duration of 192 wk (maximum total duration, 204 wk; Canada, France, Germany, Italy, Mexico, Poland, Spain, Sweden, and Switzerland) conducted between September 2010 and December 2015 24 mg/m^2 BSA (up to 40 mg) adalimumab EOW
Papp et al[5]; NCT01251614	2017	Chronic pediatric plaque psoriasis	≥4 to <18	111†	Randomized, double-blind, multicenter study (Belgium, Canada, Chile, Czech Republic, Germany, Hungary, Italy, Mexico, Netherlands, Poland, Spain, Switzerland, and Turkey) conducted between December 2010 and February 2015 Period A: initial treatment, adalimumab 0.8 mg/kg, 0.4 mg/kg, or methotrexate for 16 wk; early escape to period D option available up to wk 8; at wk 16, responders enter period B and nonresponders enter period D Period B: withdrawal, lasting no longer than 36 wk; at point of loss of disease control, patients enter period C; patients who do not lose control of their disease enter period D and remain off treatment Period C: retreatment, double-blind treatment with adalimumab for 16 wk (patients receive same randomized adalimumab dose as in period A, patients randomized to methotrexate receive 0.8 mg/kg adalimumab) Period D: long-term follow-up treatment with adalimumab for up to 52 wk
Hyams et al[6]; NCT00409682; IMAgINE I	2012	Moderate-to-severe pediatric CD	6-17	192	Randomized, double-blind multicenter study (Belgium, Canada, France, Netherlands, Poland, United Kingdom, and US) conducted between April 2007 and May 2010 Weight-based, open-label induction regimen of adalimumab at wk 0 and 2 (160 and 80 mg, respectively, if ≥40 kg; 80 and 40 mg if <40 kg) with subsequent randomization to 1 of 2 weight-based treatment arms of maintenance adalimumab: High-dose group: 40 mg EOW if ≥40 kg or 20 mg EOW if <40 kg at wk 4 Low-dose group: 20 mg EOW if ≥40 kg or 10 mg EOW if <40 kg at wk 4 At wk 26, maintenance dosing adjusted for patients whose body weight increased from <40 to ≥40 kg
Faubion et al[7]; NCT00686374; IMAgINE II extension study	2017	Moderate- to-severe pediatric CD	7-18	100	Patients who successfully completed IMAgINE I and responded to treatment received weight-based open-label adalimumab maintenance therapy for up to 408 wk; study started May 2008 Patients enrolled from double-blind therapy in IMAgINE I; patients ≥40 kg received 40 mg adalimumab EOW and patients <40 kg received 20 mg adalimumab EOW Patients who enrolled from open-label therapy in IMAgINE I continued to receive 40 or 20 mg EW

BSA, body surface area; *EOW*, every other week; *EW*, every week.
*≥4 y and weight <15 kg.
†114 patients enrolled; however, only 111 patients received a dose of adalimumab and were included in the pediatric psoriasis data analysis.

Table II. Demographics, concomitant therapy, and adalimumab exposure

Baseline characteristics	JIA (n = 274)	Pediatric psoriasis (n = 111)	Pediatric CD (n = 192)	Total (n = 577)
Mean age, y	10.7	13.0	13.6	12.1
Mean disease duration,* y	3.2	5.0	3.0	3.5
Female, n (%)	198 (72.3)	62 (55.9)	84 (43.8)	344 (59.6)
Received previous anti-TNF,† n (%)	0	11 (9.9)	84 (43.8)	95 (16.5)
Concomitant therapy‡				
Immunomodulating agents,§ n (%)	154 (56.2)	1 (0.9)	126 (65.6)	281 (48.7)
Systemic corticosteroids,¶ n (%)	117 (42.7)	4 (3.6)	104 (54.2)	225 (39.0)
Adalimumab exposure				
PY	806.9	121.5	512.3	1440.7
Median duration of exposure, PY	2.9	1.1	1.2	1.6
Maximum duration of exposure, PY	6.9	1.7	7.7	7.7
>2-y exposure, n (%)	172 (62.8)	0	82 (42.7)	254 (44.0)
>5-y exposure, n (%)	63 (23.0)	0	51 (26.6)	114 (19.8)

*JIA, n = 273; total, n = 576.
†Previous anti-TNF use was an exclusion criterion in the JIA studies; in pediatric psoriasis, previous anti-TNF use was excluded with the exception of etanercept (but not allowed within 4 weeks of baseline); in pediatric CD, previous infliximab use was allowed (but not within 8 wk of baseline).
‡At baseline and/or during the study.
§Including methotrexate, sulfasalazine, and hydroxychloroquine for JIA; mesalazine (for colitis that manifested >70 days after last dose of adalimumab) for psoriasis; and azathioprine, 6-mercaptopurine, or methotrexate for CD.
¶For JIA, changes in concomitant corticosteroid use were not permitted during the blinded portions of any study but changes were possible in open-label extension studies; for psoriasis, corticosteroid use was not permitted during the study but 4 patients received short courses of therapy for medical conditions other than psoriasis (bronchial obstructive syndrome, bronchospasm, upper respiratory tract infection, and preplanned cosmetic surgery); for CD, corticosteroids could be discontinued in IMAgINE I and II studies.

headache (24%; 19.9 events/100 PY; **Table IV**; available at www.jpeds.com). Within each indication, the most commonly reported individual AEs were injection-site pain (22% of patients; 74.7 events/100 PY) in patients with JIA; headache (30%; 46.9 events/100 PY) in patients with psoriasis; and worsening of CD (55%; 36.7 events/100 PY) in patients with CD (**Table IV**).

Rates of AEs of special interest were generally low (**Table III**). Allergic reactions occurred in 15% of patients with JIA (7.7 events/100 PY), 6% of patients with psoriasis (7.4 events/100 PY), and 10% of patients with CD (4.9 events/100 PY). Oral candidiasis and tuberculosis (TB; including active and latent) each occurred in 1% of patients across all indications (0.6 events/100 PY and 0.4 events/100 PY, respectively); notably, only 1 patient had active TB (<0.1 events/100 PY). This case of disseminated TB occurred in a male patient with ERA from Mexico with a history of latent TB at baseline; the patient enrolled on TB prophylaxis (confirmed compliance with 7 months of isoniazid). After >2.5 years on study, at age 19 years, symptomatic miliary TB was diagnosed. Adalimumab was discontinued permanently; after successful treatment for TB, he was doing well as of last follow-up, approximately 1 year later. The investigator and the sponsor considered the event probably related to the study drug.

Other opportunistic infections occurred in 1% of patients across all indications (0.3 events/100 PY), and herpes zoster occurred in 3% of patients across all indications (1.5 events/100 PY). Of the 19 patients with 21 herpes zoster events, 3 patients had serious events; all 3 patients recovered after treatment with acyclovir and did not receive further prophylaxis.

Overall, injection-site reactions were reported in 37% of patients with JIA (104.6 events/100 PY), 10% of patients with psoriasis (14.0 events/100 PY), and 22% of patients with CD (20.3 events/100 PY; **Table III**); most injection-site reaction events (>95%) were considered by the investigator to be mild or moderate. One patient with CD discontinued study drug due to an injection-site reaction while receiving open-label adalimumab.

Worsening or new onset of psoriasis occurred in 4% of patients overall (1.7 events/100 PY); rates in JIA, pediatric CD, and pediatric psoriasis were 0.7, 1.4, and 9.1 events/100 PY, respectively. Uveitis occurred in 1% of patients overall (0.6 events/100 PY); there were no events in pediatric patients with psoriasis, and rates in JIA and pediatric CD were 0.7 and 0.4 events/100 PY, respectively. There were no malignancies reported. In addition, there were no cases of demyelinating disorders, reactivation of hepatitis B, or Stevens–Johnson syndrome.

Serious Adverse Events

SAEs occurred in 29% of all patients (19.6 events/100 PY). Rates of SAEs in pediatric patients with JIA, psoriasis, and CD were 13.5, 7.4, and 32.2 events/100 PY, respectively (**Table V**). Serious infections were the most frequent SAEs across indications (8% of all patients; 4.0 events/100 PY). The rates of serious infections in patients with JIA, psoriasis, and CD were 2.7, 0.8, and 6.6 events/100 PY, respectively, including typical CD-related complications such as abdominal and anal abscess in patients with CD. CD-related complications (2 events of anal abscess and 1 event each of pelvic abscess, peritonitis, abdominal abscess, and perirectal abscess) accounted for 6 of the 20 events of serious infection that occurred after 500 days of therapy in patients with CD. Pneumonia was the most commonly reported serious infection (1% of all patients; 0.6 events/100 PY). The risk of first serious infection remained stable for the duration of the study for all indications (**Figure 2**).

Other common SAEs included exacerbation of the underlying disease (**Table IV**). For example, worsening of CD accounted for nearly one-half of the SAEs among patients with CD (15.4 events/100 PY). SAEs of diffuse vasculitis and

Table III. Overview of AEs in adalimumab pediatric clinical trials*

	JIA (n = 274)		Pediatric psoriasis (n = 111)		Pediatric CD (n = 192)		Total (n = 577)	
Adverse event (AE)	**No. (%)**	**Events (events/100 PY)**	**No. (%)**	**Events (events/100 PY)**	**No. (%)**	**Events (events/100 PY)**	**No. (%)**	**Events (events/100 PY)**
Exposure, PY	NA	806.9	NA	121.5	NA	512.3	NA	1440.7
Any AEs	267 (97.4)	4239 (525.3)	100 (90.1)	630 (518.5)	189 (98.4)	2902 (566.5)	556 (96.4)	7771 (539.4)
AE related to study drug†	200 (73.0)	1536 (190.4)	48 (43.2)	176 (144.9)	115 (59.9)	621 (121.2)	363 (62.9)	2333 (161.9)
Serious AEs	67 (24.5)	109 (13.5)	8 (7.2)	9 (7.4)	92 (47.9)	165 (32.2)	167 (28.9)	283 (19.6)
Severe AE	45 (16.4)	67 (8.3)	17 (15.3)	24 (19.8)	67 (34.9)	114 (22.3)	129 (22.4)	205 (14.2)
AE leading to discontinuation	24 (8.8)	31 (3.8)	3 (2.7)	3 (2.5)	61 (31.8)	77 (15.0)	88 (15.3)	111 (7.7)
AE leading to death	0	0	1 (0.9)	1 (0.8)	0	0	1 (0.2)	1 (<0.1)
Infection	224 (81.8)	1216 (150.7)	82 (73.9)	205 (168.7)	145 (75.5)	676 (132.0)	451 (78.2)	2097 (145.6)
Serious infection	21 (7.7)	22 (2.7)	1 (0.9)	1 (0.8)	25 (13.0)	34 (6.6)	47 (8.1)	57 (4.0)
Herpes zoster	8 (2.9)	9 (1.1)	3 (2.7)	3 (2.5)	8 (4.2)	9 (1.8)	19 (3.3)	21 (1.5)
Oral candidiasis	2 (0.7)	2 (0.2)	0	0	3 (1.6)	6 (1.2)	5 (0.9)	8 (0.6)
Any parasitic infection	3 (1.1)	5 (0.6)	0	0	1 (0.5)	1 (0.2)	4 (0.7)	6 (0.4)
TB	3 (1.1)	3 (0.4)	2 (1.8)	2 (1.6)	1 (0.5)	1 (0.2)	6 (1.0)	6 (0.4)
Active	1 (0.4)	1 (0.1)	0	0	0	0	1 (0.2)	1 (<0.1)
Latent	2 (0.7)	2 (0.2)	2 (1.8)	2 (1.6)	1 (0.5)	1 (0.2)	5 (0.9)	5 (0.3)
Opportunistic infection (excluding TB and oral candidiasis)‡	0	0	0	0	4 (2.1)	4 (0.8)	4 (0.7)	4 (0.3)
Injection-site reaction§	101 (36.9)	844 (104.6)	11 (9.9)	17 (14.0)	42 (21.9)	104 (20.3)	154 (26.7)	965 (67.0)
Allergic reaction¶	41 (15.0)	62 (7.7)	7 (6.3)	9 (7.4)	19 (9.9)	25 (4.9)	67 (11.6)	96 (6.7)
Hematologic disorders**	10 (3.6)	16 (2.0)	2 (1.8)	3 (2.5)	27 (14.1)	36 (7.0)	39 (6.8)	55 (3.8)
Worsening/new onset of psoriasis	5 (1.8)	6 (0.7)	10 (9.0)	11 (9.1)	6 (3.1)	7 (1.4)	21 (3.6)	24 (1.7)
Intestinal stricture	0	0	0	0	7 (3.6)	8 (1.6)	7 (1.2)	8 (0.6)
Intestinal perforation	0	0	0	0	2 (1.0)	2 (0.4)	2 (0.3)	2 (0.1)
Uveitis	4 (1.5)	6 (0.7)	0	0	1 (0.5)	2 (0.4)	5 (0.9)	8 (0.6)
Liver event††	5 (1.8)	5 (0.6)	0	0	1 (0.5)	1 (0.2)	6 (1.0)	6 (0.4)
Vasculitis	1 (0.4)	2 (0.2)	0	0	0	0	1 (0.2)	2 (0.1)
Noncutaneous	1 (0.4)	2 (0.2)	0	0	0	0	1 (0.2)	2 (0.1)
Cutaneous	0	0	0	0	0	0	0	0
CHF	1 (0.4)	1 (0.1)	0	0	0	0	1 (0.2)	1 (<0.1)
Lupus-like reaction and systemic lupus erythematosus	0	0	0	0	1 (0.5)	1 (0.2)	1 (0.2)	1 (<0.1)
Pancreatitis	0	0	0	0	1 (0.5)	1 (0.2)	1 (0.2)	1 (<0.1)
Malignancy	0	0	0	0	0	0	0	0

NA, not applicable.

*Serious and nonserious events are included. There were no cases of demyelinating disorders, reactivation of hepatitis B, pulmonary embolism, Stevens–Johnson syndrome, erythema multiforme, legionella, diverticulitis, progressive multiforme leukoencephalopathy, sarcoidosis, autoimmune hepatitis, cerebrovascular accident, interstitial lung disease, or reversible posterior leukoencephalopathy. The numbers of AEs (most notably allergic reactions) in the current analysis of pediatric CD differ from the report by Faubion et al[7] because of methodology. Safety outcomes in Faubion et al were derived from adjudication of standardized *Medical Dictionary for Regulatory Activities* version 13.1 search results using a January 31, 2015 cut-off date; here, data are based on company-defined search criteria of *Medical Dictionary for Regulatory Activities* version 18.1 using a December 31, 2015 cut-off date.

†As assessed by the investigator.

‡Includes 1 event each of *Aeromonas* infection, fungal esophagitis, histoplasmosis disseminated, and esophageal candidiasis.

§Including application-site rash, reaction, and swelling; injection-site bruising, discoloration, discomfort, erythema, hematoma, irritation, nodule, pain, paresthesia, pruritus, rash, reaction, swelling, urticaria, and warmth.

¶Reported events included eye pruritus, eyelid edema, injection-site urticaria, drug hypersensitivity, hypersensitivity, asthma, bronchospasm, wheezing, pruritus generalized, rash, rash generalized, and urticaria.

**Including anemia, cytopenia, leukopenia, lymphopenia, microcytic and macrocytic anemia, and neutropenia.

††Including hepatitis, hepatocellular injury, hepatotoxicity, and liver disorder.

Table V. SAEs occurring in ≥1% of patients in any indication across adalimumab pediatric clinical trials

	JIA (n = 274)		Pediatric psoriasis (n = 111)		Pediatric CD (n = 192)		Total (n = 577)	
SAEs	No. (%)	Events (events/100 PY)	No. (%)	Events (events/100 PY)	No. (%)	Events (events/100 PY)	No. (%)	Events (events/100 PY)
Exposure, PY	NA	806.9	NA	121.5	NA	512.3	NA	1440.7
Any SAE	67 (24.5)	109 (13.5)	8 (7.2)	9 (7.4)	92 (47.9)	165 (32.2)	167 (28.9)	283 (19.6)
SAEs occurring in ≥1% of patients in any group								
Worsening of CD*	0	0	0	0	61 (31.8)	79 (15.4)	61 (10.6)	79 (5.5)
Worsening of JIA*	16 (5.8)	23 (2.9)	0	0	0	0	16 (2.8)	23 (1.6)
Anemia	0	0	0	0	4 (2.1)	6 (1.2)	4 (0.7)	6 (0.4)
Pyrexia	2 (0.7)	2 (0.2)	0	0	2 (1.0)	2 (0.4)	4 (0.7)	4 (0.3)
Arthritis	3 (1.1)	3 (0.4)	0	0	0	0	3 (0.5)	3 (0.2)
Adenoidal hypertrophy	3 (1.1)	3 (0.4)	0	0	0	0	3 (0.5)	3 (0.2)
Tonsillar hypertrophy	3 (1.1)	3 (0.4)	0	0	0	0	3 (0.5)	3 (0.2)
Gastritis	0	0	0	0	2 (1.0)	2 (0.4)	2 (0.3)	2 (0.1)
Small intestinal obstruction	0	0	0	0	2 (1.0)	2 (0.4)	2 (0.3)	2 (0.1)
Tachycardia	0	0	0	0	2 (1.0)	2 (0.4)	2 (0.3)	2 (0.1)
Serious infections	21 (7.7)	22 (2.7)	1 (0.9)	1 (0.8)	25 (13.0)	34 (6.6)	47 (8.1)	57 (4.0)
Serious infections occurring in ≥1% of patients in any group								
Pneumonia	4 (1.5)	4 (0.5)	0	0	2 (1.0)	4 (0.8)	6 (1.0)	8 (0.6)
Appendicitis	4 (1.5)	4 (0.5)	0	0	0	0	4 (0.7)	4 (0.3)
Abdominal abscess	0	0	0	0	3 (1.6)	4 (0.8)	3 (0.5)	4 (0.3)
Herpes zoster	3 (1.1)	3 (0.4)	0	0	0	0	3 (0.5)	3 (0.2)
Anal abscess	0	0	0	0	3 (1.6)	3 (0.6)	3 (0.5)	3 (0.2)
Gastroenteritis	0	0	0	0	2 (1.0)	2 (0.4)	2 (0.3)	2 (0.1)
Subcutaneous abscess	0	0	0	0	2 (1.0)	2 (0.4)	2 (0.3)	2 (0.1)

*Worsening refers to worsening of the underlying disease.

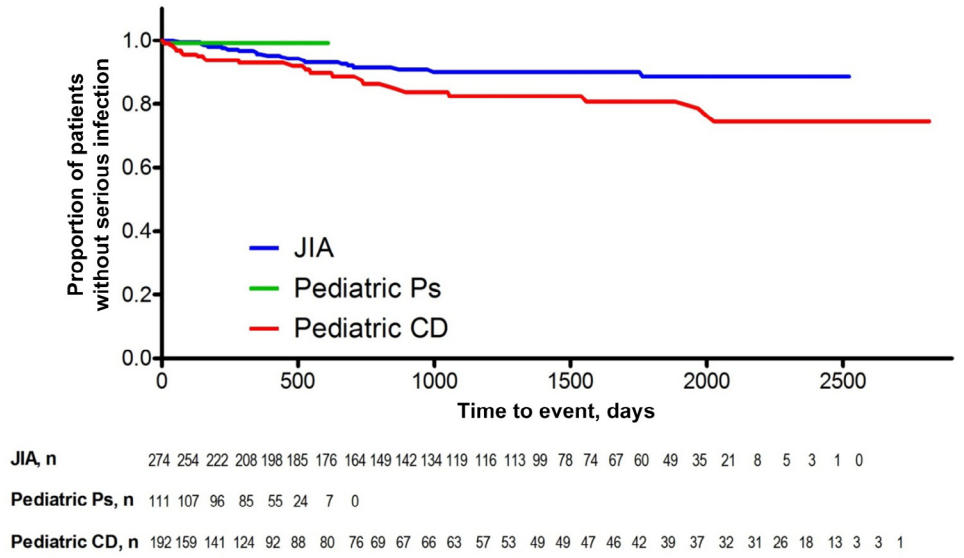

Figure 2. Time to first serious infection, by indication. Shown are patients with JIA (*blue line*), Ps (*green line*), and CD (*red line*). The first quartile, median, and third quartile are not estimable based on the data. *JIA*, juvenile idiopathic arthritis (includes patients with pJIA and ERA); *n*, patients at risk; *Ps*, psoriasis.

congestive heart failure (CHF) occurred in a 16-year-old female patient with ERA. The event of CHF occurred in conjunction with pneumonia on day 441 during a complex hospitalization subsequent to the diagnosis of diffuse vasculitis on day 433. Adalimumab was discontinued because of these events. The investigator considered the event of diffuse vasculitis probably related and the events of CHF and pneumonia probably not related to study drug. One death, due to an accidental fall, occurred in an adolescent patient with psoriasis.

AEs by Concomitant Corticosteroid Use

Greater incidences and rates of infections were observed in patients who received concomitant systemic corticosteroids vs those who did not in the overall study population (84% [158.5 events/100 PY] vs 75% [134.4 events/100 PY], respectively) as well as among patients with JIA (87% [169.6 events/100 PY] vs 78% [134.7 events/100 PY]), psoriasis (100% [196.4 events/100 PY] vs 73% [167.2 events/100 PY), and CD (79% [143.6 events/100 PY] vs 72% [116.4 events/100 PY]); of note, only 4 patients with psoriasis received systemic corticosteroids (**Table VI** and **Table VII**; available at www.jpeds.com). Similarly, incidences and rates of serious infections were greater among patients who received concomitant systemic corticosteroids vs those who did not, with the exception of patients with psoriasis, in whom serious infections were rare (1 event in a patient not receiving concomitant corticosteroids).

Growth

In patients with pJIA, long-term treatment with adalimumab was associated with improvement and maintenance of growth among patients in the ≤33rd percentile group for baseline height (n = 73) and improved pJIA signs and symptoms regardless of baseline growth status.[19] In the CD study, adalimumab significantly normalized the growth rate by week 26 (median height velocity z score, −0.34) and week 52 (0.21; both $P < .001$) in patients with baseline growth impairment (n = 73).[18] Linear growth remained stable over time in patients without baseline growth impairment (n = 27).

Discussion

The current analysis adds to a more complete understanding of the established safety profile of adalimumab and demonstrated that in pediatric patients with pJIA, ERA, psoriasis, and CD, the overall safety profile was comparable and consistent with that in adults. This analysis included patients with medium to long-term exposure to adalimumab (median duration of exposure 1.1-2.9 years across indications) and collectively represents the largest number of pediatric patients exposed to adalimumab for the longest length of time to date.

The most commonly reported individual AEs were upper respiratory tract infections, nasopharyngitis, and headache, which are not unusual in the pediatric population. The incidence and types of AEs and SAEs varied by disease, with markedly greater rates of SAEs (48%) and serious infections (13%) reported among patients with pediatric CD; however, some of these AEs may be related to a greater infection risk with CD itself[20-22] or worsening of CD. Similar to our findings, the collective safety data from an analysis of adults receiving adalimumab showed a greater rate of serious infections among patients with CD relative to other indications[10]; of note, some of the serious infections in our current analysis are common complications of CD (eg, abscesses).

There is a known risk of infection associated with anti-TNF therapy.[23,24] In this study, the risk of serious infections remained stable throughout the study for all indications. This

is consistent with adult populations, in which treatment with adalimumab resulted in a generally stable risk of serious infections across multiple indications.[10] Furthermore, the rates of serious infection observed with adalimumab treatment in pediatric patients with JIA (including pJIA and ERA) and CD were comparable with those reported in studies of adult patients with rheumatologic diseases (including rheumatoid arthritis, ankylosing spondylitis, and nonradiographic axial spondyloarthritis) and CD.[25,26] Importantly, no increased risk was observed for overall AEs or infections in patients with pJIA who transitioned into adulthood during therapy with adalimumab (n = 51).[27]

The rate of serious infection in the general pediatric population (aged 0-14 years) has been reported to be approximately 1% per year.[28,29] A systematic review of anti-TNF therapy in pediatric inflammatory bowel disease indicated that the serious infection rate with anti-TNF treatment was comparable with that of immunomodulators but was significantly lower than the expected rate with corticosteroid treatment in pediatric patients.[30] In this analysis, differences in SAEs, particularly infections, between patient populations may have occurred in part because of differences in the use of concomitant immunosuppressive medications; an analysis by immunosuppressant use was not conducted. However, patients who received concomitant systemic corticosteroids had a greater incidence and rate of infections and serious infections compared with patients who did not.

In the absence of head-to-head trial data, it is helpful to consider safety data for other anti-TNF agents with pediatric indications. Etanercept is approved for the treatment of pJIA in patients ≥2 years of age in the European Union and the US; pediatric psoriasis in patients ≥6 and ≥4 years of age in the European Union and the US, respectively; and ERA in patients ≥12 years of age in the European Union.[31-34] Rates of SAEs with etanercept were reported in a registry study (n = 594, including pJIA [90% of patients] and systemic JIA) and an open-label extension of a randomized study (n = 58; 58% with pJIA) of up to 8 years; rates were 7.1 and 12.3/100 PY, respectively.[31,33,35] The open-label extension reported a rate of 4/100 PY for serious infections.[35] For psoriasis, a randomized study of 210 pediatric patients who received etanercept reported an exposure-adjusted SAE rate of 0.6/100 PY (excluding infections); for serious infections, the rate was 1.8/100 PY.[32] A total of 8 SAEs (including 2 patients with infectious events) were reported during the open-label extension, of which only 1 (cellulitis) was considered treatment-related.[36] Infliximab is approved for the treatment of moderate to severely active CD in pediatric patients who did not respond to conventional therapy.[37] In the 54-week REACH study (a randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF chimeric monoclonal antibody [infliximab, REMICADE] in pediatric subjects with moderate-to-severe CD, N = 103), incidence rates of SAEs and serious infections were 15% and 7%, respectively,[38] whereas incidence rates of 33% and 10% were reported in the open-label extension study (N = 60), with most patients having <3 years of exposure.[39]

Registry data documenting patients treated with adalimumab for JIA in routine clinical practice are available.[11-13] The rates of AEs and SAEs were 64.5 and 4.9 events/100 PY, respectively, for patients treated with adalimumab ± concomitant therapy (eg, nonsteroidal anti-inflammatory drugs, corticosteroids, methotrexate, and other disease-modifying antirheumatic drugs) in an interim analysis (n = 552, 679 PY of exposure) of the Biologika in der Kinderrheumatologie Register (BIKER) JIA registry.[11] Similarly, in the 6-year interim analysis of the STRIVE registry, a multicenter, longitudinal postmarketing, observational study to assess long-term safety and effectiveness of HUMIRA (adalimumab; AbbVie Inc, North Chicago, Illinois) in children with moderately to severely active polyarticular or polyarticular-course juvenile idiopathic arthritis, patients with pJIA treated with adalimumab ± methotrexate (n = 543) had observed rates of AEs and SAEs of 43.7 and 7.5 events/100 PY, respectively.[13]

Opportunistic infections, excluding oral candidiasis and TB, were low in our analysis, consistent with findings in adults treated with adalimumab across multiple indications,[10] and occurred only in pediatric patients with CD. Opportunistic infections are generally rare in pediatric patients treated with TNF inhibitors based on previous studies.[11,33,38,39] Worsening/new onset of psoriasis was observed in 4% of all pediatric patients treated with adalimumab in our study. In an interim analysis of multiple therapies, 6 cases of new-onset psoriasis were observed in pediatric patients with JIA treated with adalimumab ± concomitant therapy in the BIKER registry (n = 552); this event was not observed in patients receiving other therapies (etanercept [n = 2000], tocilizumab [n = 108]), or methotrexate [n = 1517]).[11] In the present analysis, the rate of uveitis in pediatric patients treated with adalimumab was low across indications (0.6 events/100 PY) and among patients with JIA (0.7 events/100 PY). It should be noted that uveitis is comorbid of JIA. In an analysis of the BIKER registry, the rate of uveitis was 5.4 events/100 PY for patients with JIA treated with adalimumab ± concomitant therapy.[11] In the 6-year interim analysis of the STRIVE registry of pJIA, 13% of patients (68/543) treated with adalimumab ± methotrexate reported uveitis (including 42 patients with uveitis present at registry entry and 26 patients with first documentation of uveitis postenrollment).[40] Most patients in the STRIVE registry had no new onset of uveitis or had stabilized uveitis. The beneficial role of adalimumab for JIA-associated uveitis was demonstrated in the randomized-controlled trial of the clinical effectiveness, SafetY and Cost effectiveness of Adalimumab in combination with MethOtRExate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE); adalimumab treatment controlled inflammation and led to a lower rate of treatment failure vs placebo in patients with JIA-associated uveitis taking methotrexate.[41]

Although this analysis provides important data on the safety of adalimumab in pediatric populations, some limitations must be considered. For example, there were relatively low numbers of patients in certain age groups (eg, <4 years old), as well as in certain disease indications (eg, ERA), limiting conclusions for these groups. In addition, further follow-up is warranted

to assess the impact of longer treatment exposure for certain AEs (such as malignancies), compare safety between prepubertal and pubertal children, and collect long-term immunogenicity data across pediatric indications. Furthermore, because of differences between study populations (underlying diseases, concomitant medications, adalimumab dose, and/or duration of exposure), no direct statistical comparisons across indications were performed; overall comparisons across indications require caution. The safety analysis also is limited by the paucity of placebo-controlled studies, in part due to the withdrawal design of several studies,[3,4] and that non–AbbVie-sponsored clinical trials were not included, such as the controlled SYCAMORE trial.[41] Finally, longer-term data were obtained from open-label extension studies, which may select for patients who tolerate therapy. Notably, vaccination data were not captured uniformly among all studies of the current analysis. Available data from patients with pJIA support routine immunization of patients receiving adalimumab despite a perceived reluctance to do so.[42] ■

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Reprint requests: Gerd Horneff, MD, Asklepios Klinik Sankt Augustin, Arnold-Janssen-Straße 29, Sankt Augustin 53757, Germany. E-mail: g.horneff@asklepios.com

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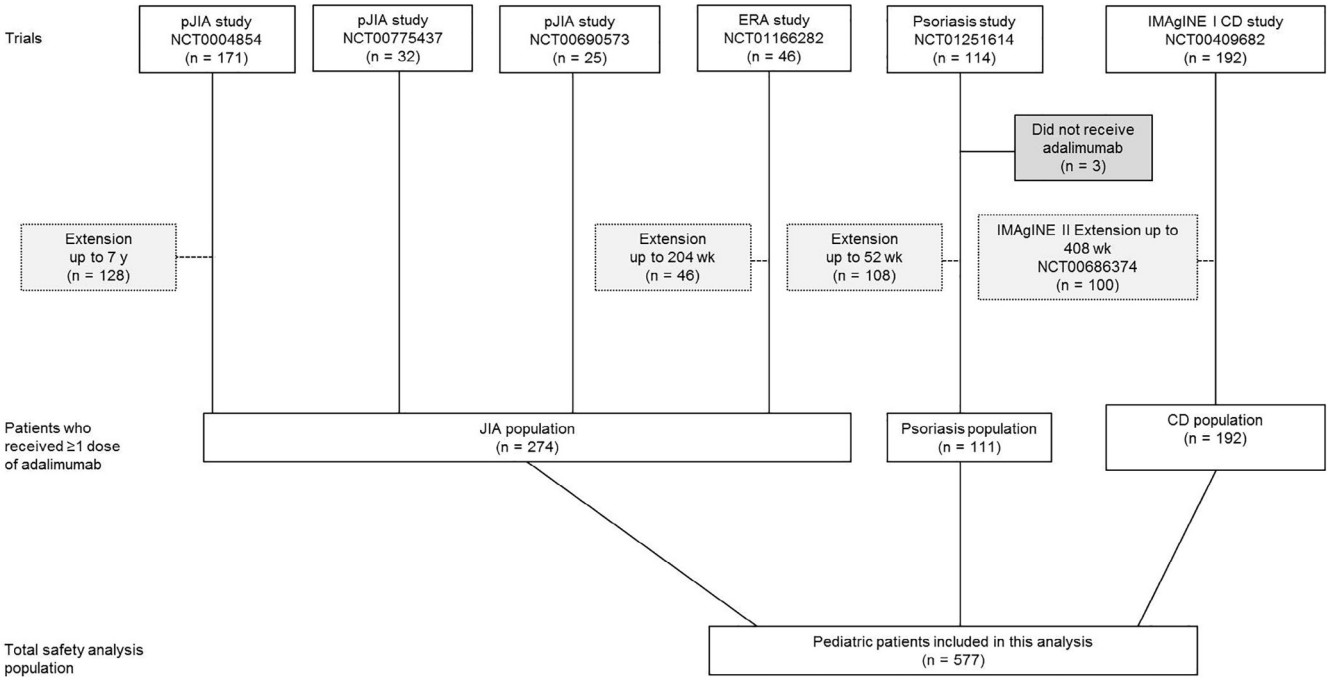

Figure 1. Safety analysis population.

Table IV. Individual AEs occurring in ≥10% of patients in any indication across adalimumab pediatric clinical trials

	JIA (n = 274)		Pediatric psoriasis (n = 111)		Pediatric CD (n = 192)		Total (n = 577)	
AEs	No. (%)	Events (events/100 PY)	No. (%)	Events (events/100 PY)	No. (%)	Events (events/100 PY)	No. (%)	Events (events/100 PY)
Exposure, PY	NA	806.9	NA	121.5	NA	512.3	NA	1440.7
Injection-site pain	61 (22.3)	603 (74.7)	5 (4.5)	6 (4.9)	15 (7.8)	37 (7.2)	81 (14.0)	646 (44.8)
Upper respiratory tract infection	94 (34.3)	244 (30.2)	20 (18.0)	30 (24.7)	43 (22.4)	76 (14.8)	157 (27.2)	350 (24.3)
Headache	53 (19.3)	110 (13.6)	33 (29.7)	57 (46.9)	51 (26.6)	120 (23.4)	137 (23.7)	287 (19.9)
Nasopharyngitis	60 (21.9)	100 (12.4)	39 (35.1)	71 (58.4)	41 (21.4)	78 (15.2)	140 (24.3)	249 (17.3)
Injection-site reaction	42 (15.3)	176 (21.8)	4 (3.6)	7 (5.8)	22 (11.5)	41 (8.0)	68 (11.8)	224 (15.5)
Worsening of CD*	0	0	0	0	106 (55.2)	188 (36.7)	106 (18.4)	188 (13.0)
Nausea	34 (12.4)	55 (6.8)	16 (14.4)	19 (15.6)	32 (16.7)	68 (13.3)	82 (14.2)	142 (9.9)
Pyrexia	41 (15.0)	53 (6.6)	8 (7.2)	11 (9.1)	35 (18.2)	67 (13.1)	84 (14.6)	131 (9.1)
Pharyngitis	41 (15.0)	70 (8.7)	7 (6.3)	9 (7.4)	20 (10.4)	48 (9.4)	68 (11.8)	127 (8.8)
Viral infection	50 (18.2)	99 (12.3)	1 (0.9)	1 (0.8)	22 (11.5)	25 (4.9)	73 (12.7)	125 (8.7)
Abdominal pain	27 (9.9)	33 (4.1)	6 (5.4)	6 (4.9)	30 (15.6)	69 (13.5)	63 (10.9)	108 (7.5)
Arthralgia	30 (10.9)	56 (6.9)	6 (5.4)	7 (5.8)	27 (14.1)	43 (8.4)	63 (10.9)	106 (7.4)
Cough	34 (12.4)	46 (5.7)	13 (11.7)	15 (12.3)	28 (14.6)	43 (8.4)	75 (13.0)	104 (7.2)
Diarrhea	30 (10.9)	35 (4.3)	7 (6.3)	8 (6.6)	35 (18.2)	54 (10.5)	72 (12.5)	97 (6.7)
Vomiting	32 (11.7)	35 (4.3)	10 (9.0)	12 (9.9)	30 (15.6)	49 (9.6)	72 (12.5)	96 (6.7)
Oropharyngeal pain	26 (9.5)	28 (3.5)	9 (8.1)	11 (9.1)	34 (17.7)	56 (10.9)	69 (12.0)	95 (6.6)
Sinusitis	34 (12.4)	46 (5.7)	3 (2.7)	3 (2.5)	20 (10.4)	38 (7.4)	57 (9.9)	87 (6.0)
Rash	40 (14.6)	46 (5.7)	2 (1.8)	2 (1.6)	18 (9.4)	28 (5.5)	60 (10.4)	76 (5.3)
Worsening of JIA*	45 (16.4)	73 (9.0)	0	0	0	0	45 (7.8)	73 (5.1)
Contusion	29 (10.6)	56 (6.9)	4 (3.6)	4 (3.3)	8 (4.2)	12 (2.3)	41 (7.1)	72 (5.0)
Upper abdominal pain	14 (5.1)	17 (2.1)	8 (7.2)	14 (11.5)	22 (11.5)	36 (7.0)	44 (7.6)	67 (4.7)
Gastroenteritis	32 (11.7)	42 (5.2)	4 (3.6)	4 (3.3)	11 (5.7)	14 (2.7)	47 (8.1)	60 (4.2)
Fatigue	12 (4.4)	14 (1.7)	8 (7.2)	11 (9.1)	25 (13.0)	31 (6.1)	45 (7.8)	56 (3.9)
Constipation	12 (4.4)	13 (1.6)	1 (0.9)	1 (0.8)	22 (11.5)	34 (6.6)	35 (6.1)	48 (3.3)

*Worsening refers to worsening of the underlying disease.

Table VI. Overview of infections and serious infections by concomitant systemic corticosteroid use

	JIA (n = 274)		Pediatric psoriasis (n = 111)		Pediatric CD (n = 192)		Total (n = 577)	
AEs, n (%)	**With (n = 117)**	**Without (n = 157)**	**With (n = 4)**	**Without (n = 107)**	**With (n = 104)**	**Without (n = 88)**	**With (n = 225)**	**Without (n = 352)**
Any infection	102 (87.2)	122 (77.7)	4 (100)	78 (72.9)	82 (78.8)	63 (71.6)	188 (83.6)	263 (74.7)
Infections in >10% of patients in the total groups								
Upper respiratory tract infection	48 (41.0)	46 (29.3)	1 (25.0)	19 (17.8)	23 (22.1)	20 (22.7)	72 (32.0)	85 (24.1)
Nasopharyngitis	29 (24.8)	31 (19.7)	0	39 (36.4)	23 (22.1)	18 (20.5)	52 (23.1)	88 (25.0)
Viral infection	26 (22.2)	24 (15.3)	0	1 (0.9)	16 (15.4)	6 (6.8)	42 (18.7)	31 (8.8)
Influenza	16 (13.7)	9 (5.7)	1 (25.0)	9 (8.4)	15 (14.4)	2 (2.3)	32 (14.2)	20 (5.7)
Pharyngitis	18 (15.4)	23 (14.6)	1 (25.0)	6 (5.6)	10 (9.6)	10 (11.4)	29 (12.9)	39 (11.1)
Sinusitis	12 (10.3)	22 (14.0)	0	3 (2.8)	15 (14.4)	5 (5.7)	27 (12.0)	30 (8.5)
Gastroenteritis	18 (15.4)	14 (8.9)	1 (25.0)	3 (2.8)	7 (6.7)	4 (4.5)	26 (11.6)	21 (6.0)
Rhinitis	13 (11.1)	12 (7.6)	2 (50.0)	5 (4.7)	8 (7.7)	4 (4.5)	23 (10.2)	21 (6.0)
Urinary tract infection	14 (12.0)	7 (4.5)	0	2 (1.9)	9 (8.7)	7 (8.0)	23 (10.2)	16 (4.5)
Infections of special interest								
Oral candidiasis	1 (0.9)	1 (0.6)	0	0	2 (1.9)	1 (1.1)	3 (1.3)	2 (0.6)
Herpes zoster	5 (4.3)	3 (1.9)	0	3 (2.8)	6 (5.8)	2 (2.3)	11 (4.9)	8 (2.3)
Any parasitic infection	3 (2.6)	1 (0.6)	0	0	1 (1.0)	0	4 (1.8)	1 (0.3)
TB								
Active	0	1 (0.6)	0	0	0	0	0	1 (0.3)
Latent	0	1 (0.6)	1 (25.0)	1 (0.9)	1 (1.0)	0	2 (0.9)	2 (0.6)
Opportunistic infection (excluding TB and oral candidiasis)	0	0	2 (1.9)	2 (2.3)	0	0	2 (0.9)	2 (0.6)
Any serious infection	12 (10.3)	9 (5.7)	0	1 (0.9)	18 (17.3)	7 (8.0)	30 (13.3)	17 (4.8)
Serious infections in >1 patient in total group								
Pneumonia	3 (2.6)	1 (0.6)	0	0	1 (1.0)	1 (1.1)	4 (1.8)	2 (0.6)
Herpes zoster	3 (2.6)	0	0	0	0	0	3 (1.3)	0
Gastroenteritis	0	0	0	0	2 (1.9)	0	2 (0.9)	0
Appendicitis	2 (1.7)	2 (1.3)	0	0	0	0	2 (0.9)	2 (0.6)
Abdominal abscess	0	0	0	0	2 (1.9)	1 (1.1)	2 (0.9)	1 (0.3)
Anal abscess	0	0	0	0	2 (1.9)	1 (1.1)	2 (0.9)	1 (0.3)
Pharyngitis	0	2 (1.3)	0	0	0	0	0	2 (0.6)
Subcutaneous abscess	0	0	0	0	1 (1.0)	1 (1.1)	1 (0.4)	1 (0.3)
Urinary tract infection	1 (0.9)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.3)
Viral infection	0	1 (0.6)	0	0	1 (1.0)	0	1 (0.4)	1 (0.3)

Concomitant corticosteroid use (at baseline and/or during the study) was permitted in all studies except for psoriasis; however, 4 patients in the psoriasis study received short courses of therapy for medical conditions other than psoriasis (bronchial obstructive syndrome, bronchospasm, upper respiratory tract infection, and preplanned cosmetic surgery). For JIA, changes in concomitant corticosteroid use were not permitted during the blinded portions of any study, but changes were possible in open-label extension studies; for CD, corticosteroids could be discontinued in IMAgINE I and II studies.

Table VII. Infections and serious infections per 100 PY by concomitant systemic corticosteroid use

	JIA (n = 274)		Pediatric psoriasis (n = 111)		Pediatric CD (n = 192)		Total (n = 577)	
AEs (events/PY)	With (PY = 369.7)	Without (PY = 437.2)	With (PY = 5.6)	Without (PY = 116.0)	With (PY = 292.4)	Without (PY = 219.9)	With (PY = 667.6)	Without (PY = 773.0)
Any infection	627 (169.6)	589 (134.7)	11 (196.4)	194 (167.2)	420 (143.6)	256 (116.4)	1058 (158.5)	1039 (134.4)
Infections with >5.0 events/PY in the total group								
Upper respiratory tract infection	117 (31.6)	127 (29.0)	1 (17.9)	29 (25.0)	48 (16.4)	28 (12.7)	166 (24.9)	184 (23.8)
Nasopharyngitis	53 (14.3)	47 (10.8)	0	71 (61.2)	45 (15.4)	33 (15.0)	98 (14.7)	151 (19.5)
Viral infection	56 (15.1)	43 (9.8)	0	1 (0.9)	16 (5.5)	9 (4.1)	72 (10.8)	53 (6.9)
Influenza	16 (4.3)	12 (2.7)	1 (17.9)	10 (8.6)	23 (7.9)	2 (0.9)	40 (6.0)	24 (3.1)
Pharyngitis	27 (7.3)	43 (9.8)	1 (17.9)	8 (6.9)	19 (6.5)	29 (13.2)	47 (7.0)	80 (10.3)
Sinusitis	19 (5.1)	27 (6.2)	0	3 (2.6)	31 (10.6)	7 (3.2)	50 (7.5)	37 (4.8)
Gastroenteritis	24 (6.5)	18 (4.1)	1 (17.9)	3 (2.6)	10 (3.4)	4 (1.8)	35 (5.2)	25 (3.2)
Rhinitis	19 (5.1)	18 (4.1)	2 (35.7)	5 (4.3)	18 (6.2)	4 (1.8)	39 (5.8)	27 (3.5)
Urinary tract infection	21 (5.7)	10 (2.3)	0	2 (1.7)	13 (4.4)	8 (3.6)	34 (5.1)	20 (2.6)
Infections of special interest								
Oral candidiasis	1 (0.3)	1 (0.2)	0	0	5 (1.7)	1 (0.5)	6 (0.9)	2 (0.3)
Herpes zoster	6 (1.6)	3 (0.7)	0	3 (2.6)	7 (2.4)	2 (0.9)	13 (1.9)	8 (1.0)
Any parasitic infection	4 (1.1)	1 (0.2)	0	0	1 (0.3)	0	5 (0.7)	1 (0.1)
TB								
Active	0	1 (0.2)	0	0	0	0	0	1 (0.1)
Latent	0	1 (0.2)	1 (17.9)	1 (0.9)	1 (0.3)	0	2 (0.3)	2 (0.3)
Opportunistic infection (excluding TB and oral candidiasis)	0	0	0	0	2 (0.7)	2 (0.9)	2 (0.3)	2 (0.3)
Any serious infection	13 (3.5)	9 (2.1)	0	1 (0.9)	24 (8.2)	10 (4.5)	37 (5.5)	20 (2.6)
Serious infections with >1 event in total group								
Pneumonia	3 (0.8)	1 (0.2)	0	0	2 (0.7)	2 (0.9)	5 (0.7)	3 (0.4)
Herpes zoster	3 (0.8)	0	0	0	0	0	3 (0.4)	0
Gastroenteritis	0	0	0	0	2 (0.7)	0	2 (0.3)	0
Appendicitis	2 (0.5)	2 (0.5)	0	0	0	0	2 (0.3)	2 (0.3)
Abdominal abscess	0	0	0	0	2 (0.7)	2 (0.9)	2 (0.3)	2 (0.3)
Anal abscess	0	0	0	0	2 (0.7)	1 (0.5)	2 (0.3)	1 (0.1)
Pharyngitis	0	2 (0.5)	0	0	0	0	0	2 (0.3)
Subcutaneous abscess	0	0	0	0	1 (0.3)	1 (0.5)	1 (0.1)	1 (0.1)
Urinary tract infection	1 (0.3)	1 (0.2)	0	0	0	0	1 (0.1)	1 (0.1)
Viral infection	0	1 (0.2)	0	0	1 (0.3)	0	1 (0.1)	1 (0.1)

Concomitant corticosteroid use (at baseline and/or during the study) was permitted in all studies except for psoriasis; however, 4 patients in the psoriasis study received short courses of therapy for medical conditions other than psoriasis (bronchial obstructive syndrome, bronchospasm, upper respiratory tract infection, and preplanned cosmetic surgery). For JIA, changes in concomitant corticosteroid use were not permitted during the blinded portions of any study, but changes were possible in open-label extension studies; for CD, corticosteroids could be discontinued in IMAgINE I and II studies.