Maintenance Golimumab Treatment in Pediatric UC Patients With Moderately to Severely Active UC: PURSUIT PEDS PK Long-Term Study Results

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Background: Long-term safety, pharmacokinetics, and efficacy of open-label golimumab therapy in children with moderate–severe ulcerative colitis were evaluated.

Methods: Week-6 golimumab responders (Mayo score decrease of ≥30% and ≥3 points from baseline, rectal bleeding subscore of 0/1 or ≥1 decrease from baseline) entered the long-term extension at week 14 and received maintenance therapy (subcutaneous, q4w). Patients ≥45 kg could receive at-home treatments at week 18. Pharmacokinetic, safety, and efficacy results were summarized through week 126 (2 years).

Results: Among 35 enrolled children, 21 (60%) responded at week 6 and 20 entered the long-term extension (median age of 14.5 years and median weight of 46.1 kg). Eleven of 20 patients (55%) completed 2 years of treatment. No anaphylactic or serum sickness-like reactions, opportunistic infections, malignancies, tuberculosis, or deaths occurred. The safety profile of golimumab from weeks 14 through 126 and that observed through week 14 was generally consistent. Median trough golimumab concentrations in evaluable patients were consistent from weeks 14 (1.39, interquartile range 0.67–3.60) through 102 (1.18, 0.78–2.16), but higher at week 110 (4.10, 1.30–4.81). The incidence of antigolimumab antibodies increased from 10% (2/20) at week 30 to 25.0% (5/20) at week 126; 1 patient had neutralizing antibodies. At week 110, 50% (10/20) of patients were in remission (ie, Pediatric Ulcerative Colitis Activity Index <10). Among all enrolled patients, 28.6% (10/35) achieved remission at week 110.

Conclusions: Among children with ulcerative colitis who initially responded to golimumab induction and received q4w maintenance treatment in the long-term extension, 50% showed continued clinical benefit through 2 years. No new safety signals were observed.

Lay Summary

Among enrolled children, 21/35 responded at week 6; 20 entered the long-term extension at week 14. Clinical remission rates and clinically meaningful changes remained stable from weeks 30 to 110. No serious anaphylactic or serum sickness-like reactions, opportunistic infections, malignancies, tuberculosis, or deaths occurred.

Key Words: ulcerative colitis, clinical response, clinical remission

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Conflicts of interest: Jeffrey S. Hyams has served as an advisory board member Janssen Research & Development, LLC and Abbvie, consultant for Celgene, Boehringer-Ingleheim, Pfizer, Roche, Lily, and Allergan. Joel R. Rosh has received consultant fees from Abbvie, Bristol Meyers Squibb, Celgene, Janssen Research & Development, LLC, and Pfizer; and received research grants from AbbVie and Janssen Research & Development. Dan Turner has received consultation fee, research grant, royalties, or honorarium from Janssen Research & Development, LLC, Pfizer, Hospital for Sick Children, Ferring, MegaPharm, AstraZeneca, AbbVie, Takeda, Rafa, Boehringer Ingelheim, Biogen, Atlantic Health, and Shire. Genevieve Veereman has served as a speaker for AbbVie, Danone, and Mead Johnson, and as an advisory board member for Boehringer-Ingelheim and Celgene and received research grants from AbbVie and Janssen Research & Development, LLC. Anne M. Griffiths has served as a speaker for AbbVie and Nestle; received consultant fees from AbbVie, Celgene, Janssen Research & Development, LLC, Lilly, Merck, Pfizer, and Roche; served as an advisory board member for AbbVie and Janssen Research & Development, LLC; and received investigator-initiated research grants from AbbVie. Melvin B. Heyman has received research grants from AbbVie Pharma, Janssen Biotech, Inc, Janssen Research & Development, LLC, Genentech, Shire, Takeda, Pfizer, and Lilly. Ghassan Wahbeh has received consultant fees from AbbVie, Janssen Research & Development, LLC, and Allergan; and received research grants from AbbVie and Janssen Research & Development, LLC. Daphne Chan, Omoniyi J. Adedokun, Lakshmi Padgett, Christopher D. O'Brien, John Lynch, and Richard S. Strauss are employees of Janssen Research & Development, LLC.

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INTRODUCTION

Golimumab (Simponi, Janssen Biotech, Inc., Horsham, PA) is a monoclonal tumor necrosis factor (TNF)-antagonist antibody approved for subcutaneous (SC) injections every 4 weeks (q4w) in adults with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.[1] Golimumab also induces and maintains clinical response and remission in adults with moderate-to-severe ulcerative colitis (UC) activity.[2,3] Studies of golimumab injections in adults have demonstrated efficacy and safety similar to that of other available TNF-antagonist agents, and very good injection-site tolerability of injections q4w in adults. A study of children with pediatric juvenile idiopathic arthritis showed that golimumab was similarly well-tolerated, with a low rate of injection-site reactions (5.8% for all enrolled patients through week 16).[4]

While several biologic therapies are approved for adults with UC, infliximab remains the only approved biologic for pediatric patients with UC.[5] This phase 1b study evaluated the pharmacokinetics (PK), safety, and efficacy of golimumab in pediatric patients (≤17 years) with moderately to severely active UC. While no formal hypothesis testing was performed, we previously reported that this study in children with moderately to severely active UC receiving golimumab injections every 4 weeks (q4w) through 14 weeks met its primary objective demonstrating that the PK disposition of golimumab induction in the overall pediatric UC population was generally comparable with that of the reference adult UC population.[6] Among 35 children enrolled, 21 (60%) children achieved Mayo response (decrease by ≥30% and ≥3 points, with a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0/1)[6,7] at week 6 and 20 children entered the study extension at week 14. Further analysis showed comparable PK and exposure–response relationships between children and adults with UC supporting extrapolation of golimumab efficacy between these patient populations.[8]

The primary intent of the study extension reported here was to assess the PK, safety, and efficacy for up to an additional 2 years of open-label golimumab treatment. The results included herein summarize these study extension data (weeks 14 through 126).

METHODS

Study Design

During the PK portion of this phase 1b, multicenter, open-label study (NCT01900574),[6] all patients who were clinical responders (using the Mayo score) at week 6 could continue receiving open-label golimumab maintenance therapy (SC injection given q4w). These clinical responders had the option to enter the study extension at week 14. Patients who entered the study extension received the same therapy they received at week 10 of the PK portion of the study [body surface area-adjusted doses: 100 mg (if weight ≥45 kg) or 45 mg/m^2 (if weight <45 kg)] as these 2 dose regimens were designed to deliver similar golimumab exposures compared with those expected to be achieved in adults who receive the approved dose regimen for UC. The first study extension dose was administered at week 14.[6] Patients ≥45 kg were eligible for at-home administration starting week 18. Per protocol, all patients in the study extension could decrease their golimumab dose at week 14 or thereafter to 50 mg or 22.5 mg/m^2 at the discretion of the investigator as permitted by local regulations. A protocol-specified 1-time dose adjustment back to 100 mg or 45 mg/m^2 was permitted based on the investigator's assessment of an increase in a patient's UC disease activity. Safety measures were routinely evaluated during the study extension.

Eligibility

Clinical responders at week 6 were eligible to receive open-label golimumab maintenance therapy and had the opportunity to participate in the study extension beginning at week 14. No other eligibility criteria were prespecified by protocol for participation in the study extension.

Concomitant Medications

Concomitant UC medications permitted were 5-aminosalicylate (5-ASAs), corticosteroids (including budesonide), and immunomodulators (6-mercaptopurine, azathioprine, or methotrexate). Between weeks 0 and 6, concomitant UC medications were not to be initiated or doses increased. For patients receiving 5-ASAs at baseline, the dose was to have remained stable through week 6. For patients receiving baseline immunomodulators or corticosteroids (including budesonide), immunomodulators could be discontinued at any time during the study and corticosteroids could be tapered beginning at week 0.

Patients who lost response after week 6 were permitted to receive rescue treatment with concomitant UC therapy as clinically indicated. However, any patient who required the addition of immunomodulators (ie, 6-mercaptopurine, azathioprine, or methotrexate) or more than a single limited course (ie, 4 weeks or fewer) of corticosteroids (including budesonide) for UC was discontinued from further administration of study agent.

Safety

Patients were queried for adverse events (AEs) and concomitant medication use at each study visit. All patients were routinely assessed for tuberculosis throughout the study extension. Routine chemistry and hematology laboratory analyses were performed every 3 months.

PK and Immunogenicity

Serum PK samples were obtained every 3 months. Analyses of serum golimumab concentrations were performed

using a validated electrochemiluminescent immunoassay method on the MesoScale Discovery platform. The lowest level of quantification (LLOQ) concentration in a sample for this method was 0.03905 µg/mL at a minimum required dilution of 1:5. Analysis of antidrug antibodies (ADAs) was performed using a drug-tolerant enzyme immunoassay.[9]

Efficacy

Efficacy was assessed during the study extension every 4 weeks from weeks 14 through 110, then every 6 months thereafter using the validated Pediatric Ulcerative Colitis Activity Index (PUCAI), a noninvasive scoring system (no endoscopic evaluation required) incorporating 6 subscores.[10] The total PUCAI score ranges from 0 to 85, with scores <10 indicating clinical remission.

Changes from baseline for the PUCAI score were summarized through week 126. The proportions of patients in clinical remission (defined by PUCAI score <10) were summarized at weeks 30, 54, and 110. Proportions of patients with clinically meaningful change defined as a ≥20-point decrease from baseline in the PUCAI score,[10] a post hoc exploratory endpoint, were summarized at weeks 30, 54, and 110. Additional exploratory analyses not specified in the original Statistical Analysis Plan included summaries for (1) clinical remission assessed by age (<12, ≥12 years), body weight (<45kg, ≥45kg), and whether or not the patient was receiving corticosteroids at the beginning of the study extension, and (2) clinically meaningful change in the PUCAI score was assessed by age (<12, ≥12 years) and body weight (<45kg, ≥45kg).

Statistical Methods

Descriptive statistics were used to summarize continuous variables. Counts and percentages were used to summarize categorical variables. Demographics, baseline disease characteristics, and UC-specific concomitant medications were summarized for patients who were clinical responders at week 6 and were treated during the study extension.

Safety analyses

All treated patients in clinical response at week 6 who received at least 1 administration of golimumab (partial or complete) during the study extension were included in the safety analysis. Safety was summarized for data from week 14 through week 126. Safety was assessed by summarizing the incidences of AEs, serious AEs (SAEs), injection-site reactions, infections, and serious infections. An injection-site reaction was defined as any AE at an injection site that was identified as an injection-site reaction by the investigator. Key safety endpoints were summarized by subgroups of age (<12, ≥12 years) and body weight (<45kg, ≥45kg).

The incidence of AEs, SAEs, injection-site reactions, infections, and serious infections through the PK portion of the study through week 14 and through the subsequent 2 years of the study extension (weeks 14 through 126) was summarized to assess whether the safety profile of golimumab in UC remained similar with increased duration of exposure. Proportion of patient with antinuclear antibodies (ANA) was also assessed.

PK and immunogenicity analyses

Serum golimumab concentrations during the study extension were summarized through week 126 for all patients in clinical response at week 6 who had 1 or more blood samples obtained after the first golimumab partial or complete SC injection in the study extension. Only available data were used for the serum golimumab concentration summaries (ie, observations were not carried forward for missing data). For summary statistics of serum golimumab concentrations, concentration values below the LLOQ were treated as zero. All treated patients who had appropriate samples for the detection of antibodies to golimumab (ie, patients with at least 1 sample obtained after their first administration of golimumab during the study extension) were included in the immunogenicity analysis set.

Efficacy analyses

All treated patients in clinical response at week 6 who received at least 1 administration of golimumab (partial or complete) during the study extension were included in these analyses. The intent of these analyses in the study extension was to assess maintenance of clinical benefit through 2 years of golimumab treatment.

Treatment failure rules were not applied, however missing data rules were applied. For all analyses, patients with insufficient data for binary endpoints were considered to not have achieved their respective endpoint (ie, nonresponse imputation); for patients with insufficient data for continuous endpoints, the last available value was carried forward.

The PUCAI score was calculated if at least 3 of 6 subscores were available from the visit at which the PUCAI score was measured. For all analyses, patients who had >3 PUCAI subscores missing at a visit were considered not to be in clinical remission at that visit.

RESULTS

The study extension was conducted at sites in the United States (10 patients), France (3 patients), Germany (1 patient), Poland (3 patients), and Israel (3 patients).

The baseline demographic characteristics of the 20 patients who were in clinical response at week 6 and entered the long-term extension (Table 1) are consistent with the overall population demographic characteristics at baseline (week 0).[1] Half of the patients were female and 85% were white. Median (interquartile range) age was 14.5 (11.0–15.5) with the youngest patient entering the study extension being 7 years of age. Median (interquartile range) weight was 46.1 (33.1–56.7)

TABLE 1. Demographics, Baseline (Week 0) Disease Characteristics, and UC-Specific Concomitant Medications; Treated Patients in Study Extension

Characteristics	Golimumab (N = 20)
Sex, n (%)	
Male	10 (50.0)
Female	10 (50.0)
Race, n (%)	
White	17 (85.0)
Black or African American	0
Asian	0
American Indian or Alaska Native	1 (5.0)
Native Hawaiian or Other Pacific Islander	0
Multiple	1 (5.0)
Not reported	1 (5.0)
Ethnicity (Hispanic/Latino), n (%)	
Yes	3 (15.0)
No	15 (75.0)
Unknown	2 (10.0)
Age (yrs)	
Mean (SD)	13.3 (2.95)
Median	14.5
IQ range	(11.0; 15.5)
Range	(7; 17)
Age categories (yrs), n (%)	
<12	6 (30.0)
≥12	14 (70.0)
Weight (kg)	
Mean (SD)	51.0 (24.28)
Median	46.1
IQ range	(33.1; 56.7)
Range	(26.7; 134.0)
Weight categories (kg), n (%)	
<45	9 (45.0)
<30	3 (15.0)
≥45	11 (55.0)
UC disease duration (yrs)	
Mean (SD)	2.2 (2.37)
Median	1.2
IQ range	(0.6; 3.3)
Range	(0.2; 10.1)
Extent of disease, n (%)	
Extensive	11 (55.0)
Limited to left side of colon	9 (45.0)
Severity of UC disease, n (%)	
Moderate disease (Mayo score ≥6 to ≤10)	18 (90.0)
Severe disease (Mayo score > 10)	2 (10.0)
Mayo score	
Mean (SD)	7.9 (1.76)
Median	8.0
IQ range	(6.0; 9.0)
Range	(6; 12)
PUCAI score	
Mean (SD)	45.5 (16.69)
Median	45.0
IQ range	(35.0; 57.5)
Range	(15; 80)
CRP concentration (mg/L)	
Mean (SD)	4.8 (5.81)
Median	2.5
IQ range	(0.9; 6.0)
Range	(0.1; 18.5)
Fecal calprotectin concentration (µg/g)	
Mean (SD)	1976.4 (1891.28)
Median	1307.8
IQ range	(597.9; 2270.0)
Range	(248.7; 5871.0)
Fecal lactoferrin concentration (µg/g)	
Mean (SD)	386.1 (292.03)
Median	325.3
IQ range	(158.2; 533.7)
Range	(29.3; 1000.0)
Concomitant UC medications, n (%)	19 (95)
5-ASAs	15 (75)
Immunomodulators	13 (65)
Corticosteroids (oral or parenteral, excluding budesonide)	7 (35)
Baseline ≤1 mg/kg P.Eq	7 (35)
Baseline >1 mg/kg P.Eq	0

CRP, C-reactive protein; IQ, interquartile range; P.Eq, prednisone equivalent; yrs, years.

kg with 3 (15%) patients weighing <30 kg. Baseline Mayo and PUCAI scores are given in Table 1.

Baseline disease activity was generally consistent between patients who were in clinical response at week 6 and entered the study extension compared with the overall patient population at week 0 [10.0% had severe disease in this study (Table 1) and 14.3% had severe disease in the overall patient population[5]]. However, fewer patients who were in clinical response at week 6 and entered the study extension had extensive disease compared with the patient population at week 0 [55% (Table 1) and 71%,[5] respectively].

At baseline, 19 (95%) patients were receiving at least 1 concomitant UC medication, primarily 5-ASAs, immunomodulators, and oral or parenteral corticosteroids (excluding budesonide). Of the 7 patients receiving corticosteroids at baseline, all 7 received an average daily corticosteroid

(prednisone-equivalent) dose ≤1 mg/kg/d (Table 1). Of note, all patients who participated in this study beginning with the 14-week PK phase were naïve to TNF antagonists.

Overall, 9 (45%) of the 20 children discontinued study drug through week 126 for reasons related to lack of efficacy; 7 patients discontinued between weeks 14 and 54 and 2 discontinued after week 54 (Supplementary Fig. S1). Of these 9 patients, 6 discontinued due to unsatisfactory therapeutic response and 3 discontinued for AEs related to unsatisfactory therapeutic response (1 each for UC flare, worsening UC, or bloody diarrhea indicating a relapse of the disease). Eight patients were receiving golimumab 100 mg and 1 patient (<45 kg) who discontinued for ulcerative flare was receiving 50 mg.

Safety

During the study extension through week 126, patients received 375 total injections (162 were given at home, most of which being self-administered) (Table 2). All patients received their scheduled doses q4w except for 2 patients at week 122 who did not receive golimumab.

At week 114, 1 patient (body weight ≥45 kg) had a dose decrease from 100 to 50 mg golimumab based on the investigator's discretion per protocol. At week 126, this patient had a subsequent dose increase based on the investigation's assessment of an increase in UC disease activity.

AEs were reported in 95% (19 patients) from week 14 through week 126. The most frequently reported AEs by preferred term were UC exacerbation (50%); headache (35%); abdominal pain and upper respiratory tract infection (25% each); and diarrhea, fatigue, and nausea (20% each) (Table 2). Through week 126, 10 (50%) of 20 patients reported reasonably related AEs (ie, considered by the investigator to be possibly, probably, or very likely related to study drug, or was unknown) most commonly injection site-related or UC exacerbation.

From week 14 through week 126, the safety profile of golimumab was generally consistent with that observed through week 14 (Table 3). The proportions of patients reporting infections were greater in the study extension; however, this may be attributable to the longer follow-up period in the study extension. Post hoc results for patients by age (<12, ≥12 years), body weight (<45kg, ≥45kg), and administration (at home, by healthcare professional) categories are summarized in Table 4.

Five patients experienced 8 SAEs, the most frequently of which was UC (ie, exacerbation), reported by 3 (15%) patients. One patient discontinued golimumab due to a serious UC exacerbation. One patient reported concurrent respiratory tract and urinary tract infections, and a broken right forearm. Another patient reported anorexia and a UC flare, each during different study visits. One patient with previously noted elevated liver enzymes and a history of primary sclerosing cholangitis was hospitalized for worsening of this condition and this was considered by the investigator not to be related to study drug. A liver biopsy and magnetic resonance cholangiopancreatography scan were consistent with primary sclerosing cholangitis. The patient was treated and discharged from the hospital the next day. Liver enzyme values above the upper limit of normal were reported, but no markedly abnormal aspartate aminotransaminase, alanine aminotransferase, or bilirubin values were observed. Golimumab treatment was not interrupted due to sclerosing cholangitis.

From weeks 14 through 126, 15 of 20 (75%) patients reported infections, with upper respiratory tract infection [5 (25%)] being most frequently reported. Oral or parenteral antimicrobial treatment was required for 55% (11/20) of patients who developed infections.

TABLE 2. Number of Patients With 1 or More Treatment-Emergent AEs During the Study Extension Through Week 126

	Golimumab (N = 20)
Average duration of follow-up (weeks)	79.1
Average exposure (number of administrations)	18.8
Total number of injections	375
Any AE, n (%)	19 (95.0)
Most frequent AE by preferred term,* n (%)	
UC†	10 (50.0)
Headache	7 (35.0)
Abdominal pain	5 (25.0)
Upper respiratory tract infection	5 (25.0)
Diarrhea	4 (20.0)
Fatigue	4 (20.0)
Nausea	4 (20.0)
Anemia	3 (15.0)
Nasopharyngitis	3 (15.0)
Rectal hemorrhage	3 (15.0)
Deaths, n (%)	0
Discontinued because of or more AEs, n (%)	3 (15.0)
Serious AEs by preferred term, n (%)	5 (25.0)
UC†	3 (15.0)
Sclerosing cholangitis	1 (5.0)
Respiratory tract infection	1 (5.0)
Urinary tract infection	1 (5.0)
Forearm fracture	1 (5.0)
Decreased appetite	1 (5.0)
Infections‡, n (%)	15 (75.0)
Serious infections‡, n (%)	1 (5.0)
Neoplasms (malignant), n (%)	0
Injection-site reactions, n (%)	4 (20.0)

AE, adverse event; UC, ulcerative colitis.
*Most frequent AEs were those reported by at least 15% of patients.
†UC flare or exacerbation (eg, an increase in or worsening of diarrhea, blood in the stool, anemia, and/or abdominal pain).
‡Infection as assessed by the investigator.

The number of injections that resulted in an injection-site reaction was 21/375 (5.6%). Four (20%) patients reported 1 or more injection-site reactions, all of which were nonserious and mild. Of the 21 injections that resulted in injection-site reactions, 18 were self-administered injections and 3 were administered by a healthcare professional. No patient discontinued because of an injection-site reaction.

TABLE 3. Selected Safety Findings Through Week 14 and During the Study Extension Through Week 126

	Golimumab	
	Through Week 14 (N = 35)	Week 14 Through Week 126 (N = 20)
Mean duration of follow-up (weeks)	13.1	79.1
Mean exposure (number of administrations)	3.2	18.8
Any AE, n (%)	33 (94.3)	19 (95.0)
Deaths, n (%)	0	0
Discontinued because of 1 or more AEs, n (%)	3 (8.6)	3 (15.0)
Serious AEs, n (%)	11 (31.4)	5 (25.0)
Infections*, n (%)	13 (37.1)	15 (75.0)
Serious infections*, n (%)	0	1 (5.0)
Neoplasms (malignant), n (%)	0	0
Injection-site reactions, n (%)	6 (17.1)	4 (20.0)

*Infection as assessed by the investigator.

Two of 18 (11%) patients tested positive for ANA at baseline and week 14 and remained positive through week 126 (titer ≥1:160). No patients developed ANA antibodies during the long-term extension. No patient was positive for antidouble stranded DNA antibodies at any time.

No deaths, malignancies, opportunistic infections, tuberculosis, or anaphylactic or serum sickness-like reactions were reported from weeks 14 through 126.

A week 6 inadequate responder had improved somewhat through week 6 and continued to improve through week 10, and at the request of the investigator was granted permission to enter the study extension starting week 14. This patient was recorded as a week 6 nonresponder and safety data were collected; the patient was not included in the study extension analyses which summarize the responder population. This patient reported AEs of back pain, nasopharyngitis, and leukocyturia during the period from weeks 14 through 126. This patient had an ANA titer of 1:160 on 1 occasion during the study extension (day 206) with all subsequent values at or below 1:80 but was negative for antidouble stranded DNA antibodies during the study extension. No SAEs, serious infections, or other AEs of interest were reported, and this patient did not discontinue golimumab due to AEs.

Pharmacokinetics and Immunogenicity

Serum golimumab trough concentrations were consistent over time through week 126, except for week 110, which had a higher median concentration than expected, possibly attributable to variability given the small sample size (Fig. 1). Most patients had detectable drug levels (above the LLOQ) through week 110.

TABLE 4. Selected Safety Findings During the Study Extension Through Week 126 by Weight (<45 kg, ≥45 kg) and Age Categories (<12 yrs, ≥12 yrs) and SC Administration (at Home, Healthcare Professional)

	Golimumab (N = 20)					
	<45 kg (n = 9)	≥45 kg (n = 11)	<12 yrs (n = 6)	≥12 yrs (n = 14)	At Home (n = 10)	SC Administration by Healthcare Professional (n = 10)
Avg duration of follow-up (weeks)	86.5	72.9	80.3	78.5	87.9	70.2
Avg exposure (number of administrations)	20.8	17.1	19.0	18.6	21.3	16.2
Deaths, n (%)	0	0	0	0	0	0
Discontinued because of ≥1 AE, n (%)	2 (22.2)	1 (9.1)	1 (16.7)	2 (14.3)	0	3 (30.0)
Patients with 1 or more, n (%)						
AEs	9 (100.0)	10 (90.9)	6 (100.0)	13 (92.9)	10 (100.0)	9 (90.0)
Serious AEs	4 (44.4)	1 (9.1)	3 (50.0)	2 (14.3)	2 (20.0)	3 (30.0)
Infections*	6 (66.7)	9 (81.8)	4 (66.7)	11 (78.6)	8 (80.0)	7 (70.0)
Serious infections*	1 (11.1)	0	1 (16.7)	0	0	1 (10.0)
Neoplasms (malignant)	0	0	0	0	0	0
Injection-site reactions	1 (11.1)	3 (27.3)	0	4 (28.6)	3 (30.0)	1 (10.0)

Avg, average; yrs, years.
*Infection as assessed by the investigator.

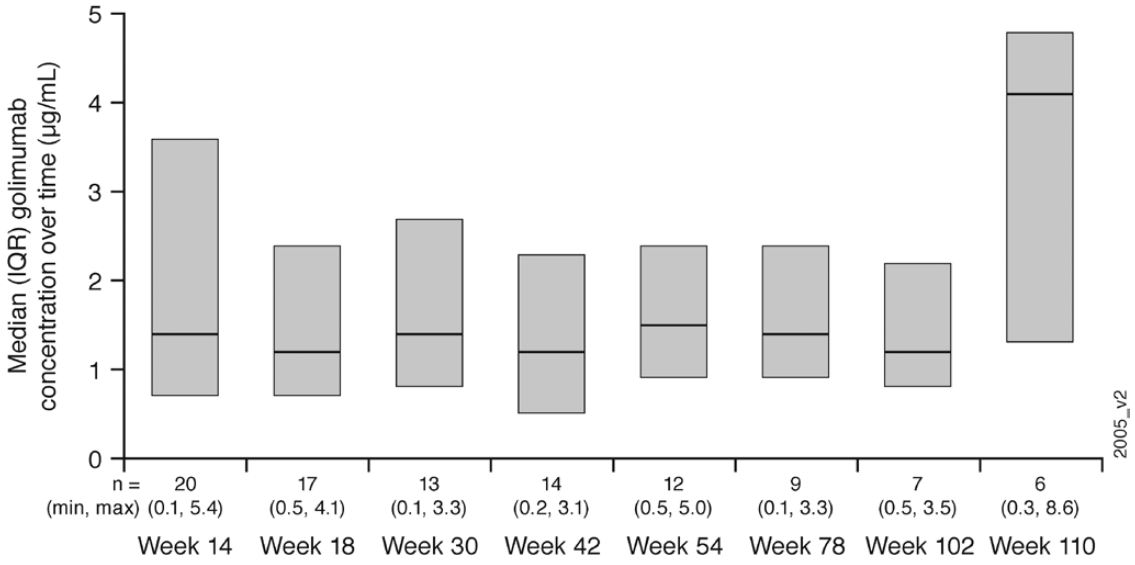

FIGURE 1. Serum golimumab concentration over time during the long-term extension study. IQR, interquartile range; max, maximum; min, minimum.

Overall, 25.0% (5/20) of patients with ≥1 sample obtained after the first golimumab administration had ADAs through week 126 or final safety visit. Three patients had titers of 1:6, 1 each had a titer of 1:24 and 1:96. Among patients positive for ADAs, 20.0% (1/5) were positive for neutralizing antibodies from weeks 14 through 126.

Efficacy

Ten of 20 (50%) patients in the study extension and 28.6% (10/35) of patients originally enrolled in this study were in PUCAI remission at week 110.

Clinical remission and clinically meaningful changes remained relatively stable after week 30 (Figs. 2A, B). The age and weight subgroup efficacy outcomes were generally consistent with those of the overall population. While a trend toward better efficacy outcomes was observed in the younger age subgroup and in the lower body weight subgroup, interpretation is limited due to the small sample size. Post hoc subgroup analyses of the proportions of patients in clinical remission among treated patients in study extension who remained steroid free were also generally consistent with the overall results for clinical remission at each time point (Fig. 2C).

The distribution of PUCAI disease severity scores over time is illustrated in Figure 3A; 85%, 65%, 75%, and 85% of patients had inactive or mild disease activity at weeks 14, 30, 54, and 126, respectively. PUCAI score median reduction from a baseline of 30 at week 14 was maintained through week 126 (Fig. 3B).

DISCUSSION

Among 35 patients enrolled and treated in the PK portion of the study, 20 patients responded to treatment at week 6 and participated in the study extension; 11 patients remained effectively on treatment through week 126. All patients entering the study extension received 1 of the 2 dose regimens [100 mg (≥45 kg) or 45 mg/m^2 (<45 kg)]. After week 18, 10 of 20 patients completed at-home administrations by self or a caregiver.

Long-term data (safety, PK, efficacy) of the pediatric population in the clinical trial setting are limited. The intent of this extension was to assess the safety, PK, and efficacy for an additional 2 years of treatment (up to week 126) with golimumab in patients who were in clinical response at week 6 and entered the study extension at week 14. The primary objective of the PK portion of this phase 1 study was met as it was demonstrated that the PK and immunogenicity profile of golimumab were comparable to the historical reference adult UC population.[6]

The overall safety profile in this study extension is consistent with that observed in the 14-week PK portion and with the known safety profile of golimumab observed in adults with UC. The most common AEs were UC exacerbation, headache, abdominal pain, and upper respiratory tract infection. During the study extension a higher proportion of patients reported nonserious infection events than during the 14-week PK phase. This finding was considered likely due to the population under study and the considerably longer exposure duration in the study extension relative to the PK phase of the study. The number of patients with ADAs was too small to draw definitive conclusions on the relationship between antibody formation and injection-site reactions.

Trough golimumab concentrations with maintenance SC golimumab treatment q4w through week 126 were consistent over the extended treatment time. A minority of patients developed ADAs, and generally were low-titer and nonneutralizing. Notably, ADA levels in this study were evaluated with a

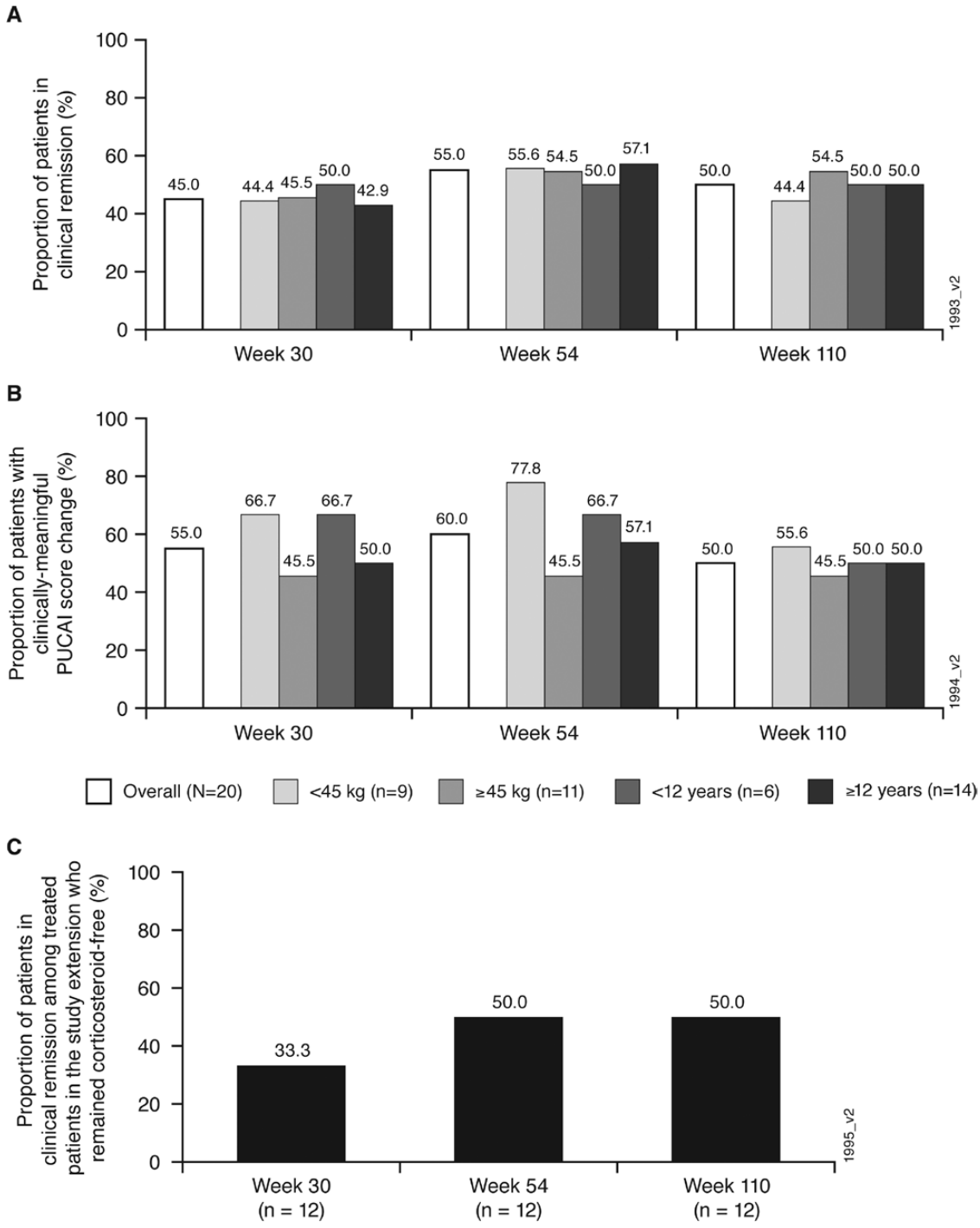

FIGURE 2. Patients in clinical remission (A), with clinically meaningful PUCAI score change (B) during the study extension, and patients in clinical remission who remained corticosteroid-free among treated patients in study extension (C). PUCAI, pediatric ulcerative colitis activity index.

drug-tolerant assay that is more sensitive than previously used assays, resulting in a higher percentage of patients with detectable antibodies than with the older methodology (results not shown). Of the 5 patients with ADAs, 3 patients had titers of 1:6, 1 patient a titer of 1:24, and 1 patient a titer of 1:96. Notably, only 1 patient had neutralizing antibodies in the study extension.

Many therapeutic proteins including infliximab are administered using an intravenous body weight (ie, mg/kg) approach that assumes drug clearance increases proportionally

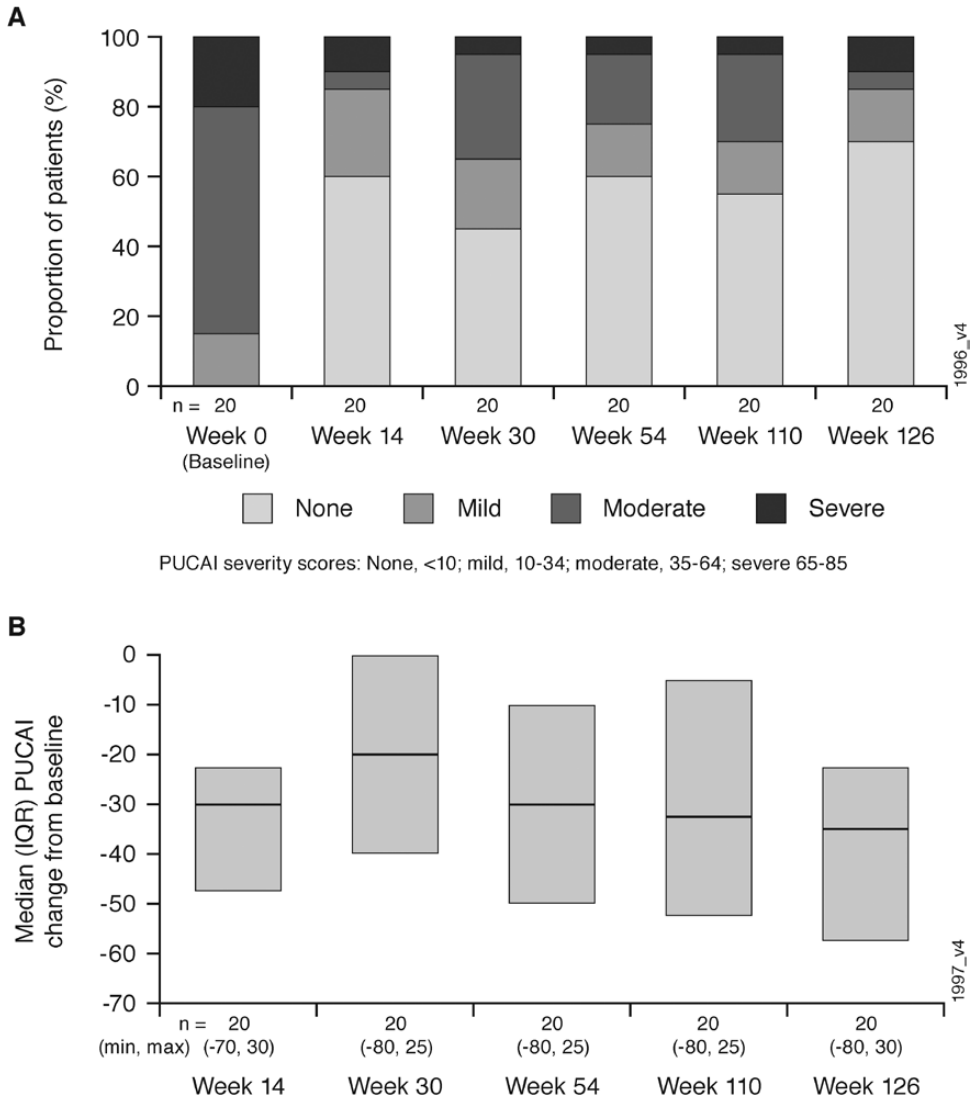

FIGURE 3. PUCAI severity distribution over time among treated patients in the study extension (A) and median PUCAI score change from baseline (B). IQR, interquartile range; PUCAI, pediatric ulcerative colitis activity index.

with body weight; however, this is not always true.[11] A separate analysis showed that because of the impact of body weight on golimumab clearance, if the same mg/kg dose was used across the pediatric age continuum, younger children and their relatively lower body weight may achieve lower-than-desired systemic exposure.[8] To mitigate the risk of underexposure associated with a mg/kg dosing scheme, a body surface area-based dose regimen was adopted for SC golimumab administration to provide a more consistent exposure in pediatric patients aged 2–17 years when compared with body weight-based dose adjustment, particularly for children with low body weight.

In the study extension, golimumab was effective in maintaining clinical remission in children with moderately to severely active UC and demonstrated continued clinical benefits in patients treated through the week 110 visit. Notably, among patients reaching the week 30 visit, few patients discontinued treatment thereafter, suggesting that rates of clinical remission and response remain relatively stable over time in patients manifesting clinical benefit at this time point. Ten of 20 (50%) patients in the study extension and 10 of 35 (28.6%) originally enrolled in this study were in PUCAI remission at week 110. This compares favorably with a 54-week, phase 3 study of infliximab 5 mg/kg in children with UC that found among week-8 Mayo score responders, more patients were in PUCAI remission at week 54 after every-8-week (8/21, 38.1%) than every-12-week (4/22, 18.2%; $P = 0.146$) therapy.[5]

Overall, clinical remission rates were consistent across analyzed subgroups of body weight, age, and whether or not the patient was receiving corticosteroids at the beginning of the study extension. A trend toward better efficacy outcomes

was observed in the younger age subgroup and in the lower body weight subgroup. Also, while the relatively small sample size of the primary population and age and weight subgroups of this study limit interpretation, the results suggest that the overall benefit of maintenance golimumab in children is at least commensurate with or better than that seen in adults.[3,12]

Important limitations of the design and conduct of the study extension should be considered. While findings are indicative of sustained clinical remission and clinically meaningful change through 2 years of follow-up in approximately half of patients responding to golimumab induction treatment, the small sample size (ie, 20 patients who responded to golimumab induction and entered the study extension among the 35 patients treated in the 14-week PK portion of this phase 1b study) and the absence of a placebo or comparator group limit our ability to draw robust conclusions on long-term efficacy or safety. Unlike the Mayo score used for adult patients with UC which includes an endoscopic evaluation for the endoscopy subscore component, our clinical outcome measure (PUCAI) is based on a noninvasive scoring system for children with UC which omits endoscopic assessments; therefore, an assessment of endoscopic healing through 2 years was not possible in this study. Eligible patients in the study extension were those identified as being in clinical response at week 6 and who did not meet withdrawal criteria by week 14 which may limit the generalizability of the findings to those who responded to and tolerated golimumab in the first 14 weeks of treatment. Finally, while patients could dose decrease during the study extension, only 1 patient did so, limiting conclusions that can be drawn from this study component on dose titration approaches for golimumab. The results from an ongoing phase 3, 54-week, pediatric trial of golimumab in patients with UC (NCT03596645) will confirm or challenge the results reported here from our limited sample size.

CONCLUSIONS

In summary, in children with moderately to severely active UC, treatment with golimumab demonstrated continued clinical benefits in approximately 50% of golimumab induction responders treated through 2 years in the open label long-term extension. The rates of clinical remission and clinically meaningful change remained stable after week 30 with few patients discontinuing therapy thereafter. The overall safety profile through 2 years of follow-up was consistent with the known safety profile of golimumab in adult patients with UC—no new safety concerns were identified in this pediatric study population.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

DATA AVAILABILITY

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson are available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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