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Intravenous Golimumab in Children With Polyarticular-Course Juvenile Idiopathic Arthritis: Long-Term Extension of an Open-Label Phase III Study

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ABSTRACT. ***Objective***. To report pharmacokinetics (PK), immunogenicity, clinical effect, and safety of intravenous (IV) golimumab in children with active polyarticular-course juvenile idiopathic arthritis (pcJIA) who participated in A Study to Evaluate the Pharmacokinetics, Efficacy and Safety of Intravenous Golimumab in Pediatric Participants With Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy (GO-VIVA)'s open-label, long-term extension (LTE) through week 252.

Methods. GO-VIVA participants who continued IV golimumab (80 mg/m^2 every 8 weeks) after week 52 were included. PK and safety were assessed through week 244 (last dose) and week 252, respectively, and clinical response through week 116. Clinical outcomes included JIA–American College of Rheumatology (ACR) responses and clinical Juvenile Arthritis Disease Activity Score in 10 joints (cJADAS10). Binary outcomes used nonresponder imputation, and other descriptive analyses used observed data.

Results. Of 112/127 (88.2%) participants entering the LTE, 69 completed the week 252 visit. Median steady-state trough golimumab concentrations were generally maintained from week 52 through week 244 (range 0.3-0.6 μg/mL). Antigolimumab antibody rates were consistent through week 52 (39.2% [49/125]) and week 244 (44.8% [56/125]). Week 52 JIA-ACR 30/50/70/90 response rates (75.6% [96/127], 74% [94/127], 65.4% [83/127], and 48.8% [62/127], respectively) were generally maintained through week 116 (72.4% [92/127], 71.7% [91/127], 63.8% [81/127], and 50.4% [64/127], respectively), when the median cJADAS10 was 1.6 and 56.7% (72/127) of participants achieved cJADAS10 ≤ 5 (minimal disease activity). Rates (per 100 patient-years) of serious adverse events and serious infections through week 252 were 7.7 and 3.9, respectively.

Conclusion. GO-VIVA LTE participants experienced adequate PK exposure and stable safety and immunogenicity. The majority of participants experienced no more than minimal residual disease activity. Data suggest IV golimumab treatment provided durable clinical response through week 116, with an acceptable risk-benefit profile.

Key Indexing Terms: biological therapy, disease-modifying antirheumatic drugs, intravenous golimumab, polyarticular-course juvenile idiopathic arthritis

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Juvenile idiopathic arthritis (JIA) is an immune-mediated arthritis of unknown etiology that persists for ≥ 6 weeks with an onset before 16 years of age.[1] JIA is classified into 7 categories: systemic JIA, rheumatoid factor (RF)-negative polyarticular JIA, RF-positive polyarticular JIA, persistent or extended oligoarticular JIA, juvenile psoriatic arthritis (PsA), enthesitis-related arthritis, and undifferentiated arthritis.[1] Polyarticular-course JIA (pcJIA), where ≥ 5 cumulative joints are affected during the first 6 months of the disease, can occur within multiple JIA categories.[1]

Recommended first-line therapy for nonsystemic polyarthritis includes nonsteroidal antiinflammatory drugs (NSAIDs) and conventional synthetic disease-modifying antirheumatic drugs (DMARDs), with intraarticular or systemic glucocorticoids (GCs), if needed, as bridging therapy.[2] Inadequately controlled active JIA and synovial inflammation can cause joint damage,[3] which can impair physical function and negatively affect quality of life.[4,5] Thus, escalation of therapy is recommended for patients with continued active disease despite first-line therapies. The availability of biologic DMARDs (bDMARDs) and targeted synthetic DMARDs increases the diversity of effective treatment options available for patients with JIA.

Intravenous (IV) golimumab, a fully human monoclonal antibody tumor necrosis factor inhibitor, is a bDMARD.[6] In the phase III study, A Study to Evaluate the Pharmacokinetics, Efficacy and Safety of Intravenous Golimumab in Pediatric Participants With Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy (GO-VIVA; ClinicalTrials.gov: NCT02277444), IV golimumab treatment through week 52 provided adequate pharmacokinetic (PK) exposure, was well tolerated, and generally reduced clinical signs and symptoms of active pcJIA.[7] After completing the week 52 study visit, GO-VIVA participants could continue to receive IV golimumab every 8 weeks (Q8W) through week 244 in a long-term extension (LTE) study.

Herein we report the PK, immunogenicity, clinical effects, and safety of IV golimumab among children with pcJIA who participated in the GO-VIVA LTE.

METHODS

Participants and study design. GO-VIVA was a phase III, open-label, single-arm, multicenter study conducted at 33 sites of the Pediatric Rheumatology Collaborative Study Group (PRCSG)[8] and the Paediatric Rheumatology International Trials Organisation (PRINTO).[9] Study details have been previously published.[7] Briefly, 127 children aged 2 to < 18 years, weighing > 15 kg, and who had a ≥ 3-month history of pcJIA manifested by ≥ 5 joints with active arthritis despite current treatment with methotrexate (MTX) for ≥ 2 months were enrolled. All participants received IV golimumab 80 mg/m^2 (maximum single dose 240 mg) at weeks 0, 4, and Q8W thereafter through week 52 (Supplementary Figure S1, available with the online version of this article). MTX was continued at the baseline dose through week 28 unless adjusted for unacceptable side effects.

Participants who completed the week 52 study visit (n = 113) could enter the LTE (week 52 to week 252), during which participants continued to receive IV golimumab 80 mg/m^2 (maximum single dose 240 mg) Q8W through week 244 with a safety follow-up visit at week 252. Participants who discontinued IV golimumab before week 244 returned for a safety follow-up visit 8 weeks after their last dose.

Statement of ethics and consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, consistent with Good

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HIB works as a full-time public employee at the Cincinnati Children's Hospital, which has received contributions from the following industries in the past 3 years: BMS, Eli Lilly, GSK, F. Hoffmann-La Roche, Janssen, Novartis, and Pfizer. This funding has been reinvested for the research activities of the hospital in a fully independent manner, without any commitment to third parties. HIB has also received consulting fees from AbbVie, AstraZeneca-Medimmune, Biogen, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, EMD Serono, Genzyme, GSK, F. Hoffmann-La Roche, Janssen, Merck, Novartis, R-Pharm, and Sanofi, and has served on speakers' bureaus for Novartis, Roche, and GSK. CPT has received speaker fees from AbbVie, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, Novartis, and Pfizer, and has served as a principal investigator for AbbVie, AstraZeneca, Biogen, Boehringer Ingelheim, Eli Lilly, Janssen, and UCB. IL has served as a consultant/advisory board member for AbbVie, Janssen, Lilly, and Pfizer. EA has received grant/research support from AbbVie, Amgen, BMS, Eli Lilly, MSD, Novartis, Pfizer, Roche, and Sanofi, and has been a speaker for AbbVie, BMS, MSD, Novartis, Pfizer, and Roche. SA has received consulting fees from AstraZeneca and GSK, and served as a principal investigator in clinical trials for BMS, Celgene, Eli Lilly, Janssen, Novartis, and Roche. AZ owns stock in Merck, OPKO Health, and Teva. DML has received consulting fees from Janssen and has served as a principal investigator for AstraZeneca, BMS, Roche, and Sobi. CER has received grant/research support (paid to institution) from AbbVie and UCB. YU has received speaker fees from AbbVie, Novartis, and Pfizer. SR, XLX, JHL, EL, and YW are employees of Janssen Research and Development, LLC, a wholly owned subsidiary of Johnson & Johnson, and may own stock or stock options in Johnson & Johnson. DJL has received grant/research support from BMS, Janssen Research and Development LLC, and Roche Laboratories; consulting fees from AstraZeneca, GSK, Novartis, Pfizer (consultant and advisory board member), and United Bioscience Corporation; and served on speakers' bureaus for Novartis and Pfizer (all above are paid to institution). AM has received consulting fees from AbbVie, Boehringer Ingelheim, Eli Lilly, EMD Serono, Idorsia, Janssen, Novartis, and Pfizer. NR received honoraria for scientific consultancies or speaker bureau participation in the past 2 years from AbbVie, Aclaris, Amgen, AstraZeneca, Aurinia, Boehringer Ingelheim, BMS, Eli Lilly, Galapagos, Guidepoint, Janssen, Novartis, Pfizer, and Sanofi. The remaining authors declare no conflicts of interest relevant to this article.

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Clinical Practice and applicable regulatory requirements. The protocol was approved by Seton Institutional Review Board (IRB) for the first site approved in the United States (approval no. CR-15-020) and by an independent ethics committee or IRB at all other sites (Supplementary Table S1, available with the online version of this article). Participants who were ≥ 7 years of age gave assent, and parents, legal guardians, or legally acceptable representatives gave written informed consent for all participants.

Assessments. During the LTE, serum golimumab concentrations were measured in samples collected at weeks 52, 100, 148, 196, and 244, or at the final safety follow-up visit, using a validated, specific, and sensitive assay.[10] The presence of antibodies to golimumab (antidrug antibodies [ADAs]), including neutralizing antibodies (NAbs), was evaluated in serum samples collected at weeks 0, 4, 8, 12, 28, 52, 100, 148, 196, and 244, or at the final safety visit using a validated, highly sensitive, drug-tolerant enzyme immunoassay with updated assay cutpoints.[11,12] Participants were classified as ADA status–positive if they had ≥ 1 ADA-positive result any time after their first golimumab administration through week 244.

The JIA core set of measures was used to assess clinical outcomes.[13] Measures included were (1) number of joints with active arthritis (characterized by swelling, or in the absence of swelling, by concurrent limited range of motion, tenderness, and/or pain on motion); (2) number of joints with limited range of motion; (3) physician global assessment (PGA) using a 0mm to 100mm visual analog scale (VAS) ranging from "no arthritis activity" to "extremely active arthritis"[13,14]; (4) functional ability, as measured by the Childhood Health Assessment Questionnaire (CHAQ), which evaluates the degree of difficulty in 8 functional areas (dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living) scored from 0 (without any difficulty) to 3 (unable to do) or not applicable to calculate a CHAQ–Disability Index (CHAQ-DI)[15-17]; (5) parent/patient global assessment (PtGA) of overall well-being, using a 0-mm (very well) to 100-mm (very poor) VAS[13]; and (6) laboratory measure of acute inflammation (for this study, serum C-reactive protein concentration was used). Parent/patient assessment of pain was evaluated using a 0-mm (no pain) to 100mm (very severe pain) VAS.[18]

Clinical outcome data were to be collected through week 244; however, because the primary aim of the study was assessment of PK and safety, a protocol amendment instituted on December 16, 2019, stopped protocol-specified collection of clinical outcome data during the LTE to allow continued treatment of participants in a manner that more closely resembled a real-world setting and reduced site data collection burden. Following implementation of this amendment, assessments and procedures were either reduced in frequency (eg, laboratory testing, vital sign measurements) or not performed/collected (eg, sexual maturity rating, clinical assessments). Timing of amendment implementation varied across countries and study sites, but for the majority of study sites, the collection of evaluable clinical outcomes data after week 116 was affected.

Safety was assessed through week 252 or at the safety follow-up visit. Safety assessments included all treatment-emergent adverse events (AEs) regardless of causality coded per the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0, and infusion reactions (any unfavorable or unintended sign that occurs during the infusion or within 1 hour of completion). Infusion reactions were evaluated in the overall population and by ADA status. Classification of AEs, including seriousness, intensity, and relation to golimumab, was determined by the investigator.

Outcomes. PK exposure outcomes were observed median steady-state trough golimumab concentrations in the overall population and by age categories (≥ 2 to < 6 years; ≥ 6 to < 12 years; ≥ 12 to < 18 years), body weight quartiles (< 29.2 kg; ≥ 29.2 kg to < 42.4 kg; ≥ 42.4 kg to < 57.0 kg; ≥ 57.0 kg), and ADA status (positive or negative).

Clinical outcomes included individual JIA core set measure scores from week 0 through week 116 and JIA–American College of Rheumatology (ACR) 30/50/70/90 criteria responses from week 4 through week 116. JIA-ACR30, JIA-ACR50, JIA-ACR70, and JIA-ACR90 are composite disease activity measures defined as at least 30%, 50%, 70%, and 90% improvement, respectively, from week 0 in ≥ 3 JIA core measures without worsening of ≥ 30% in > 1 of the remaining measures.[13] Additional outcomes included clinical Juvenile Arthritis Disease Activity Score in 10 joints (cJADAS10) values from week 0 through week 116, as well as rates of cJADAS10 disease state,[19,20] normal physical function as indicated by a CHAQ-DI score of 0,[15,17] and no more than minimal pain as indicated by a pain VAS score of < 35 mm.[18]

A composite measure of JIA disease activity, the cJADAS10 is based on the PGA, PtGA, and number of joints with active disease (maximal score of 10).[19,20] cJADAS10 disease state outcomes were minimal disease activity (MDA; cJADAS10 ≤ 5), inactive disease (ID; cJADAS10 ≤ 2.5), and remission (> 6 continuous months of cJADAS10 ID).[21]

Statistical methods. This study followed the recommendation of the Consolidated Standards of Reporting Trials statement,[22] with results reported for the full analysis set per the intention-to-treat (ITT) principle. All participants enrolled in GO-VIVA who received ≥ 1 golimumab infusion were included in analyses of clinical response and safety, and treated participants who had sufficient samples were included in PK and immunogenicity analyses. JIA-ACR responses were assessed in the ITT population and by JIA category.

Proportions of participants achieving binary outcomes are presented with 95% CIs. For the primary analysis of binary clinical outcomes, imputation rules (nonresponder imputation [NRI] for completely missing data and last observation carried forward for missing components) were used for imputing missing data. As a sensitivity analysis, binary composite clinical outcomes were analyzed using observed data. Continuous outcomes are presented as mean (SD) or median (IQR) and were determined using observed data. Safety data are presented as number of events (incidence per 100 patient-years) and number of participants (proportion).

RESULTS

Participant disposition and baseline characteristics. Of the 127 participants included in the GO-VIVA main study primary analysis set,[7] 112/127 (88.2%) continued into the LTE, 71/127 (55.9%) completed IV golimumab dosing at week 244, and 69/127 (54.3%) completed follow-up at week 252 (Figure 1). AEs were the most common reason for discontinuation through week 252, accounting for 24 of the 127 (18.9%) LTE participants.

Baseline characteristics for GO-VIVA participants have been previously published.[7] Briefly, participants were mostly White (66.9%) and female (73.2%) with a median age of 13.0 (IQR 8.0-15.0) years and weight of 42.4 kg (IQR 29.2-57.0). Most participants had RF-negative (42.5%) or RF-positive (34.6%) polyarticular JIA, whereas 9.4% had enthesitis-related arthritis, 6.3% had oligoarticular extended JIA, 3.9% had juvenile PsA, and 3.1% had systemic arthritis without systemic symptoms. Twenty-two percent of participants had received prior biologic therapy, and at baseline 72.4% were receiving NSAIDs, 37% were receiving oral GCs, and all were receiving MTX. The median cJADAS10 at baseline of 20.2 (IQR 16.9-22.9) indicated high disease activity.

PK and immunogenicity outcomes. As previously reported, the overall median steady-state trough serum golimumab concentration was stable up to week 52 and consistent across age and weight categories.[7] The week 244 observed median steady-state trough serum golimumab concentration was 0.6 μg/mL (IQR 0.2-1.0; mean 0.7 μg/mL [SD 0.6]; N = 31), which was numerically higher than the week 52 concentration of 0.4 μg/mL

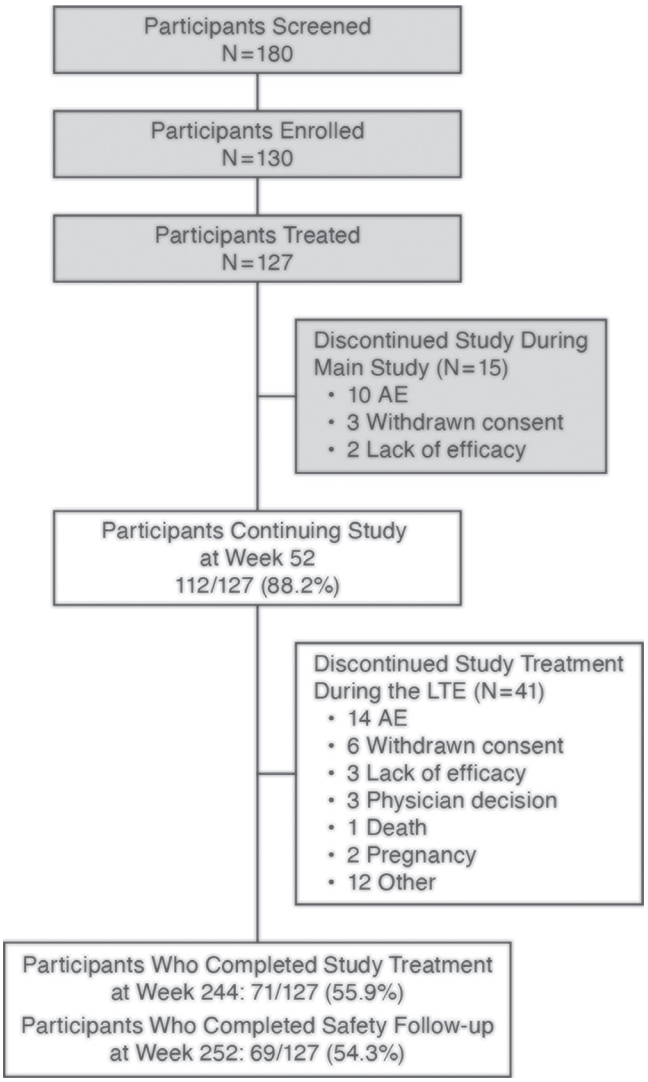

Figure 1. Participant disposition. Shaded boxes represent the main study and unshaded boxes represent the LTE. AE: adverse event; LTE: long-term extension.

(IQR 0.1-0.7; mean 0.5 μg/mL [SD 0.5]; N = 93) but within the variability range (Figure 2A). From week 52 through week 244, observed median steady-state trough serum golimumab concentrations ranged from 0.3 μg/mL (IQR 0.1-0.5) to 0.6 μg/mL (IQR 0.2-1.0), with the overlapping IQRs indicating that exposure was generally maintained. Likewise, observed golimumab exposure from week 52 through week 244 was maintained across age categories (Figure 2B) and body weight quartiles (Figure 2C). Observed median steady-state trough serum golimumab concentrations ranged from 0.3 μg/mL to 0.4 μg/mL, 0.3 μg/mL to 0.6 μg/mL, and 0.3 μg/mL to 0.6 μg/mL in participants aged ≥ 2 to < 6, ≥ 6 to < 12, and ≥ 12 to < 18 years, respectively. For participants who weighed < 29.2 kg, ≥ 29.2 kg to < 42.4 kg, ≥ 42.4 kg to < 57.0 kg, and ≥ 57.0 kg, median steady-state trough serum golimumab concentrations ranged from 0.2 μg/mL to 0.4 μg/mL, 0.4 μg/mL to 0.8 μg/mL, 0.2 μg/mL to 0.4 μg/mL, and 0.3 μg/mL to 0.7 μg/mL, respectively. Although some variability in median values was noted and despite the small number of participants within each age category and weight quartile, the overlapping IQRs surrounding the medians suggest comparable exposures across the subgroups examined.

Immunogenicity results through week 244 were consistent with those observed through week 52. Prior to entering the LTE, ADAs were detected in 49/125 (39.2%) participants with appropriate samples using a highly sensitive, drug-tolerant method; of these 49 participants, 25 (51%) were positive for NAbs, with an overall incidence of 20% (25/125). Similarly, in the LTE through week 244, ADAs were detected in 56/125 (44.8%) participants with appropriate samples; of these 56 participants, 35 (62.5%) were positive for NAbs, with an overall incidence of 28% (35/125). Six participants had a peak titer of ≥ 1000, and the highest titer was 1:12,288 in 1 participant who subsequently discontinued treatment due to serious or severe infusion reaction (hypersensitivity). Most participants positive for ADAs through week 244 had peak titers < 1:1000, including 12 with peak titer ≥ 100 to < 1000, 22 with peak titer ≥ 10 to < 100, and the remaining with peak titer < 10.

During the LTE, median trough golimumab concentrations were generally lower in ADA-positive vs ADA-negative participants (Figure 2A) and tended to decrease as peak ADA titers increased (data not shown), although the numbers of participants in the higher peak titer groups were small.

Clinical outcomes. As early as week 4 (the earliest timepoint assessed), 28.3% (36/127) of participants achieved at least JIA-ACR70 as determined using NRI (Figure 3), and median (IQR) cJADAS10 decreased to 11.8 (6.6-16.4), within the moderate disease activity range (Figure 4A). By week 52, 75.6% (96/127), 74% (94/127), 65.4% (83/127), and 48.8% (62/127) of participants achieved JIA-ACR30, JIA-ACR50, JIA-ACR70, and JIA-ACR90, respectively (Figure 3), and the median (IQR) cJADAS10 was reduced to 2.4 (0.3-7.4), generally within the MDA range (≤ 5; Figure 4A). Additionally, at week 52, 57.5% (73/127) of participants achieved cJADAS10 MDA (inclusive of ID), 44.9% (57/127) achieved cJADAS10 ID, and 26.8% (34/127) achieved cJADAS10 remission (Figure 4B).

During the LTE, JIA-ACR response rates from week 0 of the main study were generally stable through week 116 (Figure 3). At week 116, the JIA-ACR30, JIA-ACR50, JIA-ACR70, and JIA-ACR90 response rates were 72.4% (92/127), 71.7% (91/127), 63.8% (81/127), and 50.4% (64/127), respectively. Disease activity remained low during the LTE, with cJADAS10 MDA, ID, and remission response rates at 56.7% (72/127), 41.7% (53/127), and 29.1% (37/127), respectively, at week 116 (Figure 4B). Median cJADAS10 (Figure 4A) and median JIA-ACR component scores (Supplementary Table S2, available with the online version of this article) were also stable during the LTE through week 116.

Similar patterns of early and durable responses were observed for patient-reported outcomes. At week 4, 64.6% (82/127) of participants had no more than minimal pain (VAS < 35 mm) and 11.8% (15/127) had normal physical function (CHAQ-DI score of 0; Figure 5). At week 52 and week 116, 66.9% (85/127) and 33.9% (43/127) and 62.2% (79/127) and 29.1% (37/127)

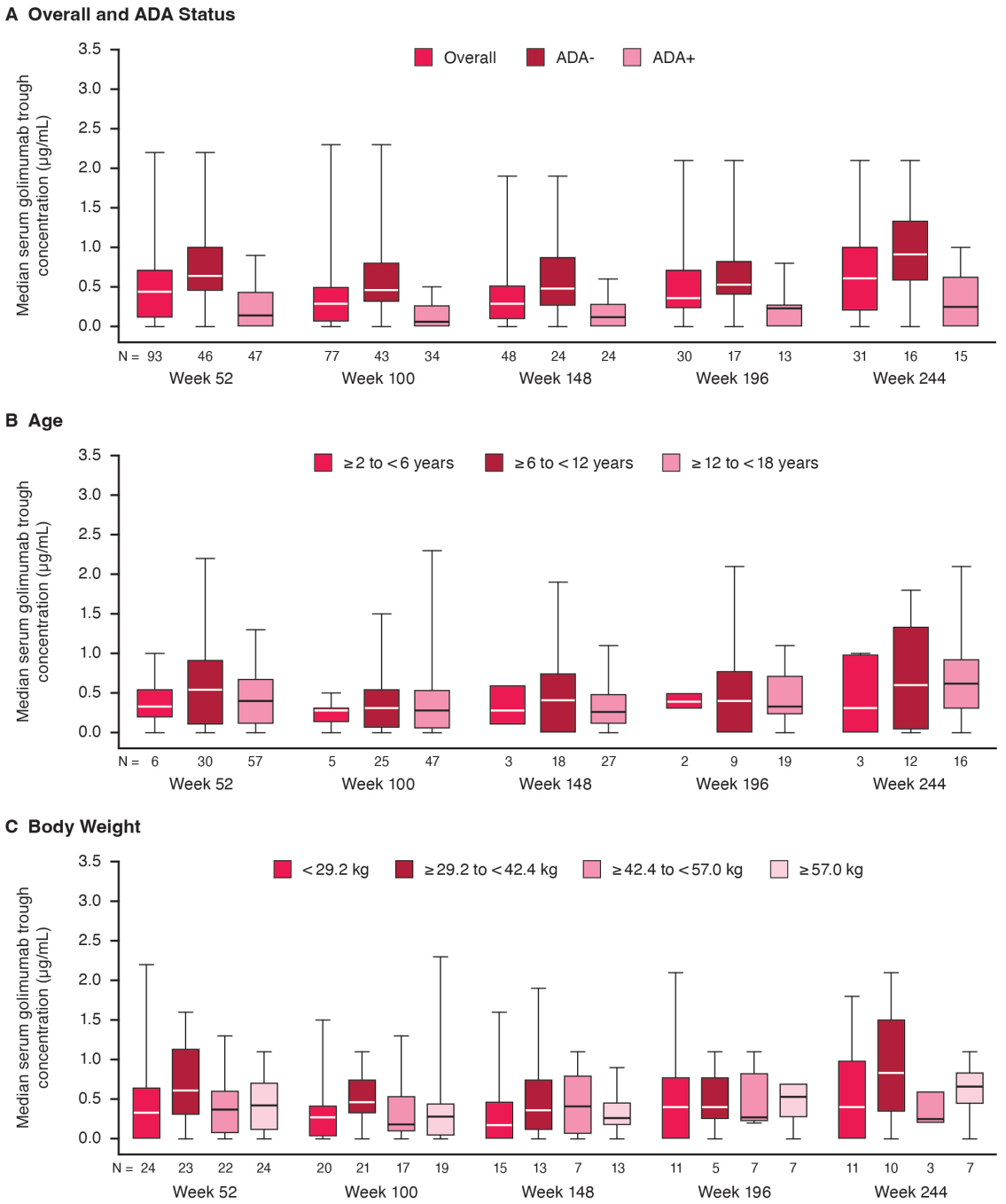

Figure 2. Median steady-state serum trough GOL concentrations during the LTE (A) in the overall population and by ADA status, (B) by age categories, and (C) by body weight quartiles. The horizontal lines within the boxes represent the medians, the lower edges of the boxes represent the first quartile, the upper edges of the boxes represent the third quartile, and the whiskers represent the range. ADA: antidrug antibodies; GOL: golimumab; LTE: long-term extension.

of participants had no more than minimal pain and normal physical function, respectively. Mean (SD) reduction in CHAQ-DI score was 0.34 (0.47) at week 4, 0.66 (0.67) at week 52, and 0.77 (0.67) at week 116 (Supplementary Figure S2, available with the online version of this article).

For all clinical outcomes, results of sensitivity analyses employing observed data showed response patterns consistent with those seen in NRI analyses (Supplementary Figures S3A-C, available with the online version of this article). JIA-ACR responses by JIA category are shown in Supplementary Table S3.

Safety outcomes. Through week 252, the rates of AEs, serious AEs (SAEs), and AEs leading to discontinuation per 100 patient-years of exposure were 207.5, 7.7, and 6.5, respectively (Table). Twenty-five of 127 participants (19.7%) had ≥ 1 SAE through week 252, including 9 participants with an SAE through week 52. All SAEs reported through week 252 occurred in 1 participant

each, except for cellulitis, pneumonia, sepsis, and varicella, each of which occurred in 2 participants. The rates of infections and serious infections per 100 patient-years were 91.6 and 3.9, respectively. A total of 105 of 127 (82.7%) participants had ≥ 1 infection, and the most common AEs were upper respiratory tract infection (29.1% [37/127]) and nasopharyngitis (23.6% [30/127]; Table). Eight participants had coronavirus disease 2019 (COVID-19) or tested positive through week 252. No COVID-19 event was considered by the investigator to be serious, of severe intensity, related to golimumab, or resulted in golimumab discontinuation. One case of active disseminated tuberculosis (TB; serious, of moderate intensity, resulted in golimumab discontinuation, event resolved) was reported in a Brazilian participant who did not have a history of active or latent TB. This participant was receiving oral corticosteroids (stopped approximately 1 year before the TB diagnosis) and MTX at a dose of 15 mg/week.

One death due to septic shock occurred after week 52.[7] Two events of systemic lupus erythematosus were reported: 1 before week 52 (nonserious, of moderate intensity, golimumab discontinued, event ongoing at last visit) and 1 after week 52 (serious, of moderate intensity, golimumab discontinued, event ongoing at last visit). Manifestations included malar rash, vasculitic lesions, and nonremitting arthritis in the first participant and polyarthralgia, oral ulcer, nose erythema, and pleural and pericardial effusions in the other. One event each of retinal vasculitis (nonserious, of moderate intensity, golimumab discontinued, event ongoing at last visit) and Crohn disease (serious, of moderate intensity, golimumab discontinued, event resolved) as well as 2 events of psoriasis (1 nonserious and of moderate intensity, 1 nonserious and of mild intensity; in both cases, golimumab was continued and the events were ongoing at last visit) were reported after week 52. Anterior uveitis (preferred term was iridocyclitis in 2 participants and uveitis in 1 participant) was reported in 3 participants through week 252 (1 before and 2 after week 52). All 3 of these participants had known uveitis risk factors; all were RF negative and antinuclear antibody positive, 2 were aged ≤ 6 years at JIA onset, 2 were female, 1 had JIA duration < 2 years, and 1 had a history of uveitis and had recently discontinued MTX. All 3 anterior uveitis events were nonserious, of mild intensity, resolved, and did not result in golimumab discontinuation.

Six participants (3/69 [4.3%] ADA negative and 3/56 [5.4%] ADA positive, 2 of whom were NAb positive) experienced 11 infusion reactions through week 252, including 4 reactions in 3 participants through week 52 (Table). Two infusion reactions led to golimumab discontinuation: hypersensitivity, occurring in an ADA-positive participant, was serious and of severe intensity; and urticaria, occurring in an ADA-negative participant, was nonserious and of moderate intensity. No other infusion reactions were serious or of severe intensity, and no cases of anaphylactic or serum sickness reactions, demyelinating events, or clinically important hepatobiliary events were reported.

DISCUSSION

We previously reported that, among children with active pcJIA despite MTX use who participated in the GO-VIVA study, IV golimumab at 80 mg/m^2 Q8W was well tolerated and provided adequate PK exposure to achieve clinical efficacy over 1 year.[7] Here, we report that, among GO-VIVA participants who continued to receive IV golimumab 80 mg/m^2 Q8W through week 252, PK exposure through week 244 was consistent with that observed at week 52. Steady-state trough serum golimumab concentrations were also consistent and similar over time across age groups and body weight quartiles from week 52 through week 244, indicating that body surface area–based dosing was appropriate to achieve similar PK exposure across the entire pcJIA age and body weight range.

Additionally, data through week 116 demonstrated that IV golimumab treatment resulted in early and durable clinical responses. Improvements in JIA-ACR scores, cJADAS, pain, and physical function were observed as early as week 4 (the earliest timepoint assessed), with a substantial proportion of participants achieving important levels of improvement at week 52 that were maintained through week 116. The improvement in clinical signs and symptoms of pcJIA observed here is consistent with that reported for subcutaneous golimumab[23] and other bDMARDs in patients with pcJIA.[24-30]

The proportion of participants who were positive for ADAs and NAbs was stable through week 244, and the majority of ADA-positive participants consistently had low peak ADA titers. Median trough serum golimumab concentrations were generally lower in participants who were ADA positive vs those who were ADA negative. The proportion of participants with infusion reactions through week 252 was similar among participants with and without ADAs.

No new safety signals were identified through week 252 of IV golimumab in this patient population, demonstrating an acceptable long-term risk-benefit profile consistent with that observed through week 52.[7] As previously described, 1 death due to septic shock occurred after week 52.[7] Despite the location of some participants in countries where TB is endemic, only 1 case of TB was reported. Overall, the safety profile of IV golimumab through week 252 in children with pcJIA was consistent with that observed with IV golimumab in adults with rheumatic disease,[31-33] with subcutaneous golimumab in patients with pcJIA,[23] and with other bDMARDs in studies of similar patient populations.[24-28,30,34]

The clinical results presented here are limited by the open-label, nonrandomized, uncontrolled, single-arm study design; the decreasing sample size over time; and the protocol modification that halted clinical assessments after week 116. However, the conservative NRI approach and the consistency of these results with analyses using observed data strengthen the findings. RF-positive JIA was overrepresented in GO-VIVA; 34.6% of participants were RF positive despite a relative frequency of 2% to 11.9% in the general population.[35] However, this category is often overrepresented in clinical trials in JIA,[23-25,29,34] most likely because these patients have a low remission rate and high disease burden.[5,36] Further, although PK results by age categories, body weight quartiles, and ADA status in the LTE were generally consistent with those of the overall population, these results should be interpreted with caution due to variable participant discontinuation rates across subgroups and the limited sample sizes for these analyses.

Future studies could assess the proportion of patients who achieve JIA-ACR inactive disease[37] and/or JIA-ACR100. In addition, given that 29.9% to 37.8% of participants had a pain score > 35 mm through week 244, evaluation of the correlation of pain score with clinical response may be warranted.

In conclusion, among participants with active pcJIA treated with IV golimumab 80 mg/m^2 Q8W, PK exposure through week 244 was consistent with that observed through week 52. Additionally, although data were limited, the stable rates of clinically important outcomes from week 52 through week 116 suggest a therapeutic benefit with continued IV golimumab treatment beyond 1 year and, in the context of the

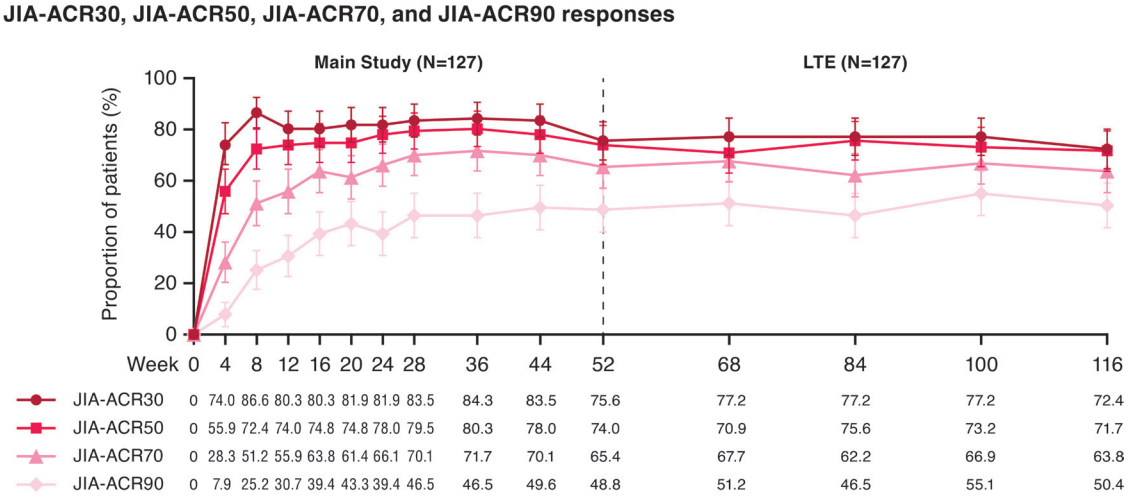

Figure 3. JIA-ACR responses from week 0 of the main study through week 116 (ITT analysis). Bars represent 95% CIs. ITT: intention to treat; JIA: juvenile idiopathic arthritis; ACR: American College of Rheumatology; LTE: long-term extension.

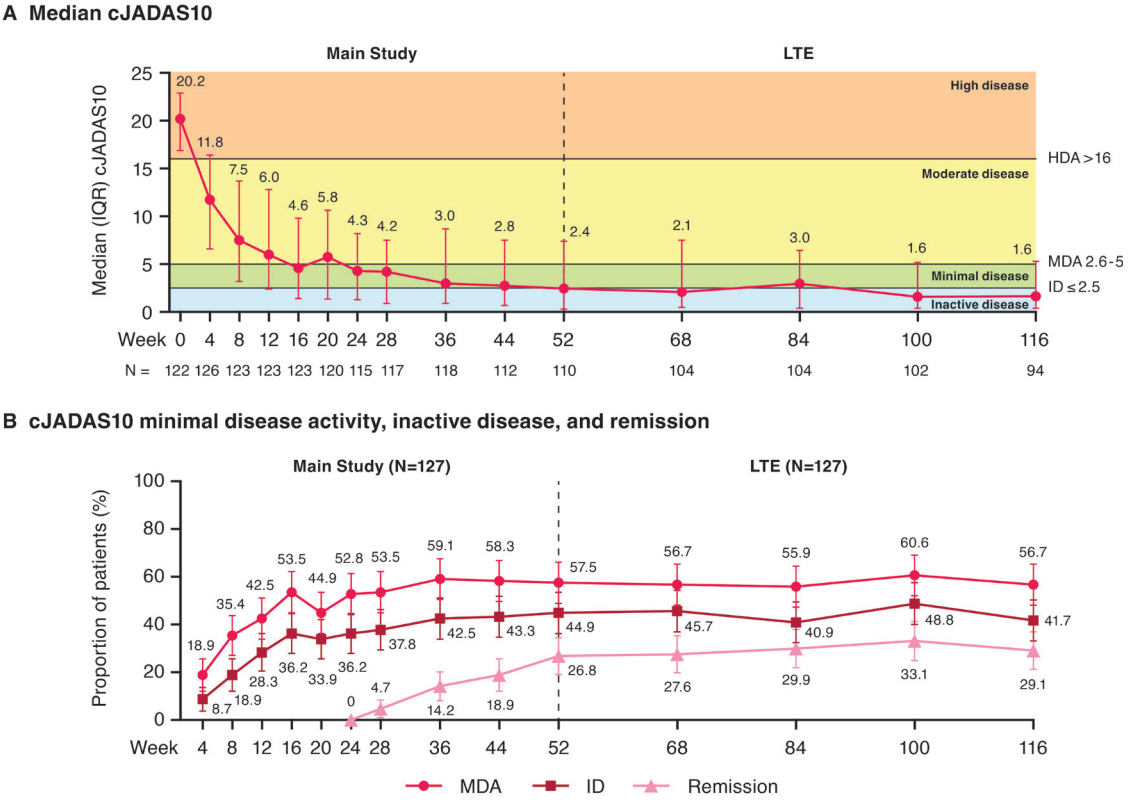

Figure 4. cJADAS10 (A) values and (B) disease states from week 0 of the main study through week 116 (ITT analysis), shown in median (IQR). Bars represent IQR in panel A and 95% CIs in panel B. HDA was defined as cJADAS10 > 16; MDA as cJADAS10 ≤ 5, inclusive of ID; ID as cJADAS10 ≤ 2.5; and remission as ≥ 6 continuous months of cJADAS10 ID (ie, cJADAS10 at ≥ 2 consecutive study assessments). cJADAS10: clinical Juvenile Arthritis Disease Activity Score in 10 joints; HDA: high disease activity; ID: inactive disease; ITT: intention to treat; LTE: long-term extension; MDA: minimal disease activity.

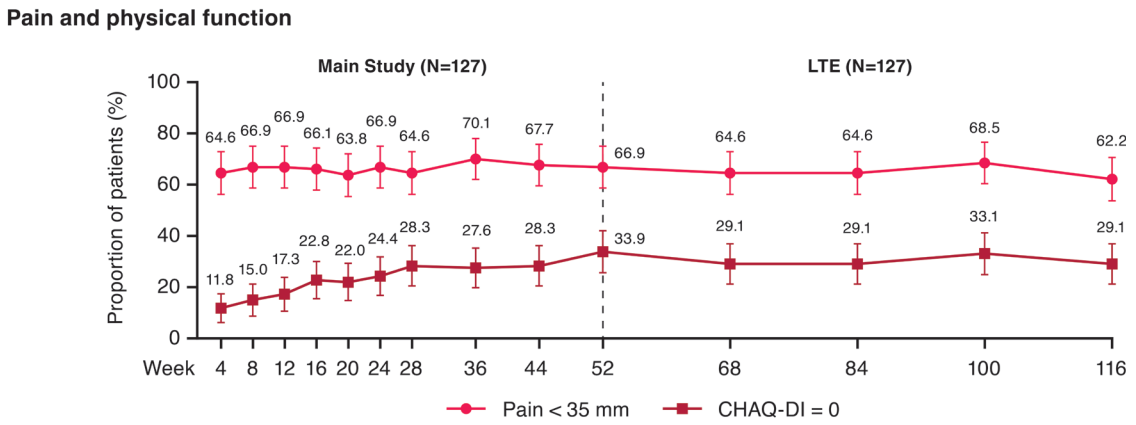

Figure 5. Rates of no more than minimal pain and normal physical function from week 0 of the main study through week 116 (ITT analysis). Bars represent 95% CIs. CHAQ-DI: Childhood Health Assessment Questionnaire–Disability Index; ITT: intention to treat; LTE: long-term extension.

long-term safety data reported here, an acceptable risk-benefit profile.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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Table. Rates of all treatment-emergent AEs through week 252.

	N = 127
Total PY of follow-up	465.1
No. of events, per 100 PY of follow-up	
Any AE	965 (207.5)
SAEs	36 (7.7)[a]
AEs leading to discontinuation	30 (6.5)
Infections[b]	426 (91.6)
Serious infections	18 (3.9)
Opportunistic infections[c]	2 (0.4)
Tuberculosis	1 (0.2)
Malignancies	1 (0.2)[d]
Infusion reactions	11 (2.4)[e]
Deaths	1 (0.2)[f]
AEs occurring in ≥ 5% of participants	
URI	37 (29.1)
Nasopharyngitis	30 (23.6)
Gastroenteritis	17 (13.4)
Urinary tract infection	12 (9.4)
Pharyngitis	11 (8.7)
Tonsillitis	10 (7.9)
Varicella	8 (6.3)
Viral URI	8 (6.3)
Respiratory tract infection	7 (5.5)
Rhinitis	7 (5.5)
Nausea	16 (12.6)
Vomiting	14 (11.0)
Abdominal pain	10 (7.9)
Upper abdominal pain	8 (6.3)
Diarrhea	8 (6.3)
JIA	28 (22.0)
Arthritis	11 (8.7)
Headache	19 (15.0)
Epistaxis	8 (6.3)
Allergic conjunctivitis	9 (7.1)
Increased ALT	8 (6.3)

Values are expressed as n (%). [a] Cellulitis, pneumonia, sepsis, and varicella (each event occurred in 2 participants), as well as disseminated tuberculosis, *Escherichia* infection, furuncle, disseminated herpes zoster, infective exacerbation of bronchiectasis, streptococcal pneumonia, septic shock, tonsillitis, constipation, Crohn disease, gastritis, calcinosis, drug intolerance, temperature regulation disorder, myopericarditis, supraventricular tachycardia, glaucoma, retinal detachment, generalized anxiety disorder, major depression, suicidal ideation, hypersensitivity, clavicle fracture, systemic lupus erythematosus, cutaneous T cell lymphoma, hydronephrosis, pleural effusion, and cyanosis (each event occurred in 1 patient). [b] Infection as assessed by investigators. [c] Opportunistic infections were identified using a standardized MedDRA version 25.0 query of opportunistic infections with the scope of narrow.[38] [d] Stable, stage 1A cutaneous T cell lymphoma (verbatim term: mycosis fungoides) reported 55 days after the third GOL infusion in a participant with a JIA duration of 0.9 years with eczema and skin lesions at study entry who had no prior biologic or Janus kinase inhibitor use and had discontinued MTX after week 8. [e] Eleven infusion reactions occurred over 10 infusions. [f] One death due to septic shock was reported at week 78. AE: adverse event; ALT: alanine aminotransferase; GOL: golimumab; JIA: juvenile idiopathic arthritis; MedDRA: Medical Dictionary for Regulatory Activities; MTX: methotrexate; PY: patient-years; SAE: serious adverse event; URI: upper respiratory tract infection.

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