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Pharmacokinetics, Pharmacodynamics, and Safety of Etrolizumab in Children With Moderately to Severely Active Ulcerative Colitis or Crohn's Disease: Results from a Phase 1 Randomized Trial

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Background: Etrolizumab, a humanized anti-β7 antibody, has not been studied in children. Here, we evaluate the pharmacokinetics, pharmacodynamics, and safety of etrolizumab in children with inflammatory bowel disease.

Methods: Patients age 4 to 17 years with moderately to severely active ulcerative colitis or Crohn's disease were randomized 1:1 to receive 1.5 mg/kg of etrolizumab subcutaneously every 4 weeks (q4w) or 3.0 mg/kg every 8 weeks (q8w) for 16 weeks in this open-label phase 1 trial. Pharmacokinetics, pharmacodynamics, safety, and efficacy were assessed.

Results: Of the 24 patients treated, 21 completed the study. In the groups of 1.5 mg/kg q4w and 3.0 mg/kg q8w, respectively, mean (SD) maximum concentration (C_{max}) was 9.8 (4.86) μg/mL and 18.1 (6.25) μg/mL; and mean (SD) area under the curve within a dosing interval (AUC_{tau}) was 167 (86.9) and 521 (306) μg · day/mL after the last dose. The C_{max} increased dose proportionally. The AUC over an 8-week period was slightly higher in the 3.0 mg/kg q8w dose group. Median half-life was similar for both dosing regimens. Median numbers of free $\beta7^{high}$ gut-homing T and B cell subsets declined below 10% of baseline, confirming β7 target engagement and complete/near-complete receptor occupancy. Adverse events were consistent with the safety profile in adults. Approximately 60% of patients achieved a clinical response.

Conclusions: Etrolizumab showed a dose-proportional increase in C_{max} and a slightly greater than dose-proportional increase in AUC_{tau}. Both regimens achieved complete/near-complete β7 receptor occupancy, with a similar relationship to concentration as adults. Etrolizumab was well tolerated and demonstrated clinical activity in children.

Key Words: biologics, IBD, Crohn's disease, inflammatory bowel disease, pediatric, pharmacokinetics, ulcerative colitis

Introduction

Etrolizumab is a next-generation, gut-targeted, anti-integrin biological therapeutic. In contrast to vedolizumab, which targets α4β7, etrolizumab is a dual-action, anti-β7 monoclonal antibody that selectively targets the α4β7 and αEβ7 integrins to control both trafficking of immune cells into the gut and their inflammatory effects on the gut lining.[1,2] In a phase 2 study of adults with moderately to severely active ulcerative colitis, etrolizumab was well tolerated and provided significantly higher rates of clinical remission following an induction regimen compared with placebo.[3] Phase 1 and 2 studies have demonstrated a dose-proportional pharmacokinetic profile of etrolizumab in adult patients with inflammatory bowel disease.[2] A population pharmacokinetic model developed from those data supported flat dosing in adults.[2,4]

Pediatric patients with inflammatory bowel disease often present with more extensive and clinically severe disease than adult patients with inflammatory bowel disease, which is known to hinder pediatric growth and development.[5,6] Adequate drug exposure is vital to achieve and maintain clinical remission.[6] Variable drug clearance among patients with inflammatory bowel disease is often associated with factors such as body size/weight, disease severity, serum albumin levels, development of antidrug antibodies, and other factors.[7,8] In addition, in the case of biological therapies for inflammatory bowel disease (such as infliximab), there is insufficient evidence to support adult-to-pediatric extrapolation of appropriate dosing regimens because of pharmacokinetic differences between children and adults.[8,9] Some studies suggest that higher concentrations of biological therapies

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(specifically adalimumab, infliximab, and vedolizumab) may be required to achieve clinical response in pediatric patients with inflammatory bowel disease.[10]

The objective of this first clinical trial of etrolizumab in pediatric patients with inflammatory bowel disease was to understand the pharmacokinetics, pharmacodynamics, and safety of etrolizumab in this population and to explore efficacy. Data from this study will inform dose selection for any future pediatric phase 3 clinical trials of etrolizumab.

Methods

Study Design

This randomized, open-label, phase 1 study (ClinicalTrials.gov, NCT03478956) was conducted at 5 sites (2 sites in Poland and 1 each in Spain, Belgium, and the United Kingdom). The study consisted of 2 phases. During the initial 24-week phase, all patients received weight-based dosing (mg/kg) of etrolizumab for 16 weeks followed by 8 weeks of safety follow-up with drug washout (where no treatment was given). Serum samples were collected during the treatment period and the safety follow-up period to enable pharmacokinetic and pharmacodynamic characterization. This 24-week phase was followed by an optional 312-week open-label extension phase of etrolizumab treatment. Patients who completed treatment (ie, only the 24-week phase or the 24-week and the open-label extension phases) or who discontinued early from the treatment phase (either the 24-week or the open-label extension phase) entered a 104-week safety surveillance phase for progressive multifocal leukoencephalopathy monitoring, during which no etrolizumab was given. We report results of the 24-week phase, which took place between March 27, 2018, and December 2, 2019.

Ethical Considerations

This trial was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The trial protocol, informed consent forms, and other relevant documents were approved by the institutional review board at each investigational site. Written informed consent was obtained from the parent or legal guardian of each participant before enrollment.

Patient Population

Eligible patients were children and adolescents age 4 to 17 years (inclusive) who weighed at least 13 kg. Patients must have received a diagnosis of moderately to severely active ulcerative colitis within 12 months before screening or moderately to severely active Crohn's disease (confirmed by biopsy) at least 3 months before screening. Moderately to severely active ulcerative colitis was defined as a Mayo Clinic total score of 6 to 12, with a Mayo endoscopic subscore of at least 2 and a rectal bleeding subscore of at least 1; moderately to severely active Crohn's disease was defined as a Pediatric Crohn's Disease Activity Index (PCDAI) higher than 30 (no endoscopy requirement). All patients must have had an inadequate response, loss of response, or intolerance to prior treatment with immunosuppressants, corticosteroids, and/or antitumor necrosis factor therapies.

Patients were excluded if they had a history or current evidence of extensive colonic mucosal dysplasia, fixed symptomatic stenosis of the intestine, or prior treatment with any anti-integrin agent (natalizumab, vedolizumab, efalizumab), ustekinumab, anti-adhesion molecules, or rituximab. Patients were also excluded if they had a history of extensive colonic surgery or planned to have surgery, past or present ileostomy or colostomy, diagnosis of indeterminate colitis, or toxic megacolon within the previous year. Patients were excluded if colectomy was imminent (ulcerative colitis), if they had short bowel syndrome, if they had evidence of abdominal or perianal abscess, or if it was suspected that surgery would be required to manage complications (Crohn's disease). Exclusion criteria also included a history of demyelinating disease; neurological conditions or diseases that could interfere with progressive multifocal leukoencephalopathy monitoring; history of major neurological disorders (eg, stroke, multiple sclerosis, brain tumor, neurodegenerative disease, poorly controlled epilepsy); evidence of or treatment for *Clostridioides difficile* within 60 days before day 1; clinically significant cytomegalovirus colitis within 60 days before day 1; or history of active or latent treated tuberculosis, regardless of treatment history. Concomitant therapy with corticosteroids (intravenous, oral, or topical), 5-aminosalicylate (oral or topical), and immunosuppressants was permitted.

Randomization and Treatments

Patients were randomly assigned in a 1:1 ratio through an interactive voice/web-based response system to receive either high-frequency etrolizumab (1.5 mg/kg once every 4 weeks [q4w]) for a total of 4 doses (weeks 0, 4, 8, and 12) or low-frequency etrolizumab (3.0 mg/kg once every 8 weeks [q8w]) for a total of 2 doses (weeks 0 and 8). Randomization was stratified by weight (<40 kg, ≥40 kg). Each patient was assigned a patient number on day 1 and was allocated to treatment using a permuted block randomization method.

Etrolizumab was administered by subcutaneous injection to the abdomen or thigh (if the abdomen was not available during the treatment period). Modifications to the dosing regimens were not allowed. Patients who experienced clinically significant worsening of ulcerative colitis or Crohn's disease could receive rescue therapy consisting of methotrexate, corticosteroids, and/or immunomodulators based on the discretion of the investigator.

Outcomes and Assessments

The primary objective was to evaluate the pharmacokinetics and pharmacodynamics of etrolizumab in pediatric patients with moderately to severely active inflammatory bowel disease. Venous blood samples for etrolizumab serum concentration were collected at days 0, 4, 28, 56, 84, 88, 98, and 112 during the treatment period. Patients in the 3.0 mg/kg q8w arm had 2 additional pharmacokinetic samples collected on days 60 and 70. During the safety follow-up period, pharmacokinetic samples were collected at days 126, 140, and 168. Antidrug antibody samples were collected at days 0, 28, 84, 112, and 168. A validated immunofluorescence assay (Gyrolab; Gyros Protein Technologies) was used to determine serum etrolizumab concentration. The minimum quantifiable concentration was 80 ng/mL. Immunogenicity was assessed through evaluation of serum samples for the presence of antidrug antibodies to etrolizumab using bridging immunoassays.

Primary pharmacokinetic outcomes were maximum concentration (C_{max}) after the first and last doses, area under the

concentration-time curve within a dosing interval (AUC_{tau}), elimination half-life, and trough concentration (C_{trough}) of etrolizumab. Noncompartmental analysis was used to derive the pharmacokinetic parameters with commercial software (WinNonlin; Pharsight Corporation, Version 6.4).

The primary pharmacodynamic outcome was β7 receptor occupancy, assessed by flow cytometry, on β7 receptor–expressing, gut-homing lymphocyte subsets in peripheral blood. Absolute numbers of free $\beta7^{high}$ gut-homing subsets, specifically CD3 T cells ($CD3^+CD45RA^-\beta7^{high}$), CD4 T cells ($CD3^+CD4^+CD45RA^-\beta7^{high}$), CD8 T cells ($CD3^+CD4^-CD45RA^-\beta7^{high}$), and CD19 B cells ($CD19^+IgD^-\beta7^{high}$) were assessed at baseline and at select postdose time points during the treatment period (days 4, 56, 84, 98, and 112) and the safety follow-up period (days 126, 140, and 168).

Safety was assessed in all patients who received at least 1 dose of the study drug. Primary safety outcomes were incidence and severity of infection-related adverse events, incidence of immunogenicity responses, and incidence and severity of hypersensitivity reaction events. Immunogenicity response was assessed in all patients who had at least 1 antidrug antibody assessment, and relationships between antidrug antibody status and safety, efficacy, and pharmacokinetic/pharmacodynamic parameters were investigated.

Efficacy outcomes were exploratory and consisted of clinical response at week 16. In patients with ulcerative colitis, clinical response was assessed with the Pediatric Ulcerative Colitis Activity Index (PUCAI) and was defined as a decrease from baseline (study day 1) of at least 20 points at week 16. In patients with Crohn's disease, clinical response was assessed with the PCDAI and was defined as a decrease from baseline (study day 1) of at least 15 points at week 16.

Postdose changes in levels of serum mucosal vascular addressin cellular adhesion molecule 1 (MAdCAM-1; an exploratory pharmacodynamic biomarker) were also assessed. Clinical biomarkers of inflammation, serum C-reactive protein, and fecal calprotectin were also assessed.

Statistical Analysis

No formal sample size and power calculations were performed for this study. Approximately 24 patients age 4 to 17 years with moderately to severely active ulcerative colitis or Crohn's disease were planned to be enrolled to target at least 12 patients with evaluable pharmacokinetic profiles, including at least 4 patients aged 4 to 11 years.

Analysis populations consisted of all patients who received at least 1 dose of study drug and had sufficient evaluable samples. The pharmacokinetic-evaluable population comprised all patients who had sufficient pharmacokinetic samples to enable the evaluation of primary pharmacokinetic parameters. Pharmacodynamic biomarker assessments included all patients who had a baseline sample measurement. The antidrug antibody incidence population comprised all patients who had at least 1 postdose antidrug antibody measurement. All pharmacokinetic parameters and pharmacodynamic measures were summarized using descriptive summary statistics.

Results

Patient Characteristics

Of 30 patients screened, 24 patients were enrolled, randomly assigned, and administered at least 1 dose of study drug; 21 patients completed the 24-week treatment phase (Figure 1). In the 1.5 mg/kg q4w dose group, 1 patient discontinued at study day 1 because of a serious adverse event (anxiety disorder); in the 3.0 mg/kg q8w dose group, 1 patient withdrew from treatment at study day 64 because of

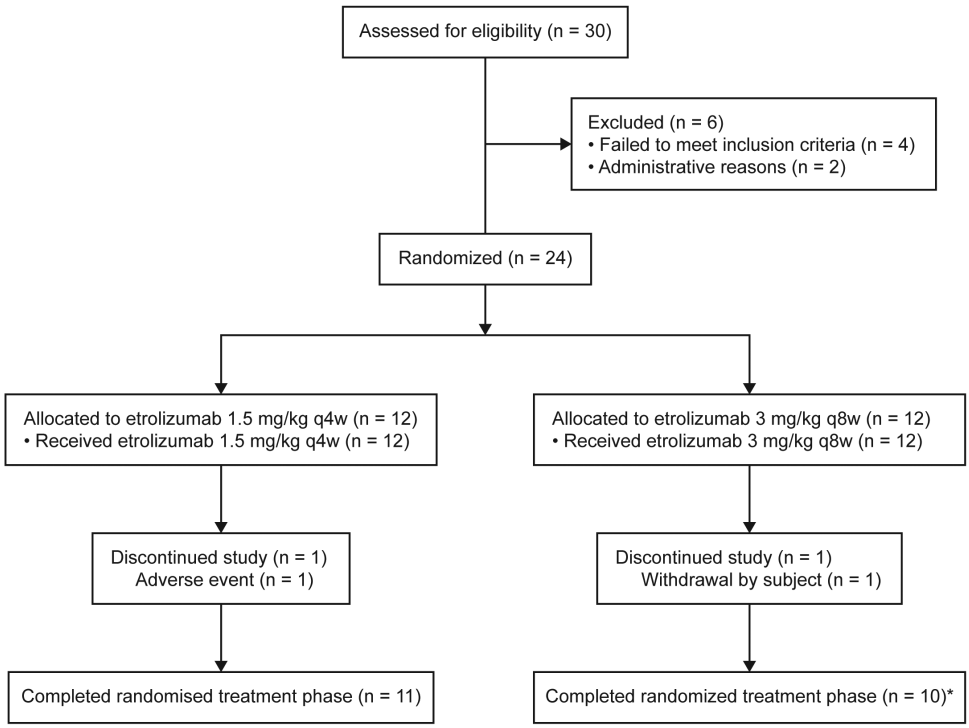

Figure 1. Study disposition. ∗Two subjects in the 3 mg/kg dose group withdrew from treatment. One subject withdrew from treatment because of an adverse event but did not withdraw from the study. Abbreviations: q4w, every 4 weeks; q8w, every 8 weeks.

a serious adverse event (exacerbation of Crohn's disease) but remained in the study, and 1 patient withdrew from the study because of a serious adverse event (exacerbation of ulcerative colitis) at day 129. The serious adverse event of anxiety disorder in the 1.5 mg/kg q4w dose group was reported by the investigator as related to etrolizumab treatment.

Demographic data and baseline characteristics were similar between dose groups (Table 1). The majority of patients were male. In both dose groups, 7 of 12 patients (58.3%) had ulcerative colitis, and 5 of 12 patients (41.7%) had Crohn's disease. Patients had a median duration of disease of 2.2 years (ulcerative colitis) and 4.4 years (Crohn's disease).

Pharmacokinetics

Of the 24 patients who received at least 1 dose of etrolizumab, 23 were included in the pharmacokinetic analysis. Concentration-time profiles following subcutaneous administration of etrolizumab at 1.5 mg/kg q4w or 3.0 mg/kg q8w are shown in Figure 2A. The concentration-time profiles of patients in the 3.0 mg/kg q8w dose group demonstrated wider interpatient variability compared with those of patients in the 1.5 mg/kg q4w dose group.

The pharmacokinetic parameters for both dose groups are summarized in Table 2. The observed C_{max} after the first and last doses was doubled following a dose of 3.0 mg/kg q8w compared with the 1.5 mg/kg q4w dose. After the first dose, mean (standard deviation [SD]) C_{max} was 7.7 (2.18) µg/mL for the 1.5 mg/kg q4w group and 19.0 (8.21) µg/mL for the 3.0 mg/kg q8w group. The mean C_{max} after the last dose was 9.8 (4.86) µg/mL and 18.1 (6.25) µg/mL for the 1.5 mg/kg q4w and 3.0 mg/kg q8w groups, respectively. Although the 2 regimens offered the same total dose over an 8-week period, mean AUC_{tau} ($AUC_{56\text{-}112}$) of the 3.0 mg/kg q8w dose group (521 µg*day/mL) was slightly more than double the AUC_{tau} ($AUC_{84\text{-}112}$) of the 1.5 mg/kg q4w dose group (167 µg*day/mL). Mean half-life was 7.3 days and 8.7 days for the 1.5 mg/kg q4w and 3.0 mg/kg q8w dose groups, respectively. Following the second dose of 1.5 mg/kg q4w, C_{trough} at week 8 (day 56) was approximately 78% higher than at week 4 (day 28) and was stable after week 8, suggesting that steady state was reached by week 8. Only 2 trough concentrations were measured following the 3.0 mg/kg q8w dose; C_{trough} at week 16 (day 112) was approximately double that of week 8.

The impact of body weight, age, and disease indication on etrolizumab pharmacokinetics was explored. A trend toward a positive correlation between body weight and drug clearance was observed for patients with body weight of less than 35 kg—but not for those with body weight of 35 kg or higher because of the wide variability in clearance measurements (Figure 2B). The mean clearance in patients age 4 to 11 years was smaller than that in patients age 12 to 18 years, although the distribution of individual clearance values largely overlapped between these 2 age groups (Figure 2C). In addition, the mean etrolizumab exposure in patients with ulcerative colitis was slightly higher than that in patients with Crohn's disease for both dose groups. However, the limited sample sizes and different body weight distributions precluded determination of the impact of disease population on etrolizumab pharmacokinetics or exposure.

Pharmacodynamics

The pharmacodynamics biomarker assessment included 21 patients; data from 3 patients were excluded because of lack of a baseline sample or samples were deemed of unacceptable quality for measurement. Following etrolizumab treatment, decreases in median absolute counts of free $\beta7^{high}$ gut-homing CD3 T cells, CD4 T cells, CD8 T cells, and CD19 B cells were observed in both dose groups. At the earliest sampling time point (day 4), the median absolute number of free $\beta7^{high}$ T and B cell subsets decreased to levels below 10% of baseline in both treatment groups, confirming etrolizumab target engagement and indicating complete or near complete occupancy of β7 receptors (Figure 3A; Figure S1). Occupancy of β7 receptors was generally maintained in both dose groups throughout the etrolizumab dosing period. Some transient loss of complete occupancy was observed in some of the gut-homing subsets before dosing; however, this transient loss returned to complete occupancy with subsequent etrolizumab dosing. In the safety follow-up period, reductions in β7 receptor occupancy were observed in all gut-homing T and B cell subsets in both dose groups at day 126 (2 weeks after the end of the 16-week exposure and

Table 1. Demographics and baseline characteristics (intent-to-treat population).

	Etrolizumab 1.5 mg/kg q4w (*n* = 12)	Etrolizumab 3.0 mg/kg q8w (*n* = 12)	All Patients (N = 24)
Age, years	12.3 (3.6)	13.4 (4.5)	12.8 (4.0)
Male	8 (66.7%)	5 (41.7%)	13 (54.2%)
Body weight, kg	43.5 (14.96)	47.6 (19.76)	45.5 (17.27)
Disease indication			
Crohn's disease	5 (41.7%)	5 (41.7%)	10 (41.7%)
Ulcerative colitis	7 (58.3%)	7 (58.3%)	14 (58.3%)
Duration of disease, years			
Crohn's disease	4.1 (1.39)	4.3 (3.73)	4.2 (2.66)
Ulcerative colitis	3.1 (3.53)	2.6 (2.20)	2.8 (2.84)
Prior corticosteroid use	6 (50.0%)	6 (50.0%)	12 (50.0%)
Prior anti-TNF use	9 (75.0%)	7 (58.3%)	16 (66.7%)

Data are mean (SD) or number (%). Abbreviations: q4w, every 4 weeks; q8w, every 8 weeks; SD, standard deviation.

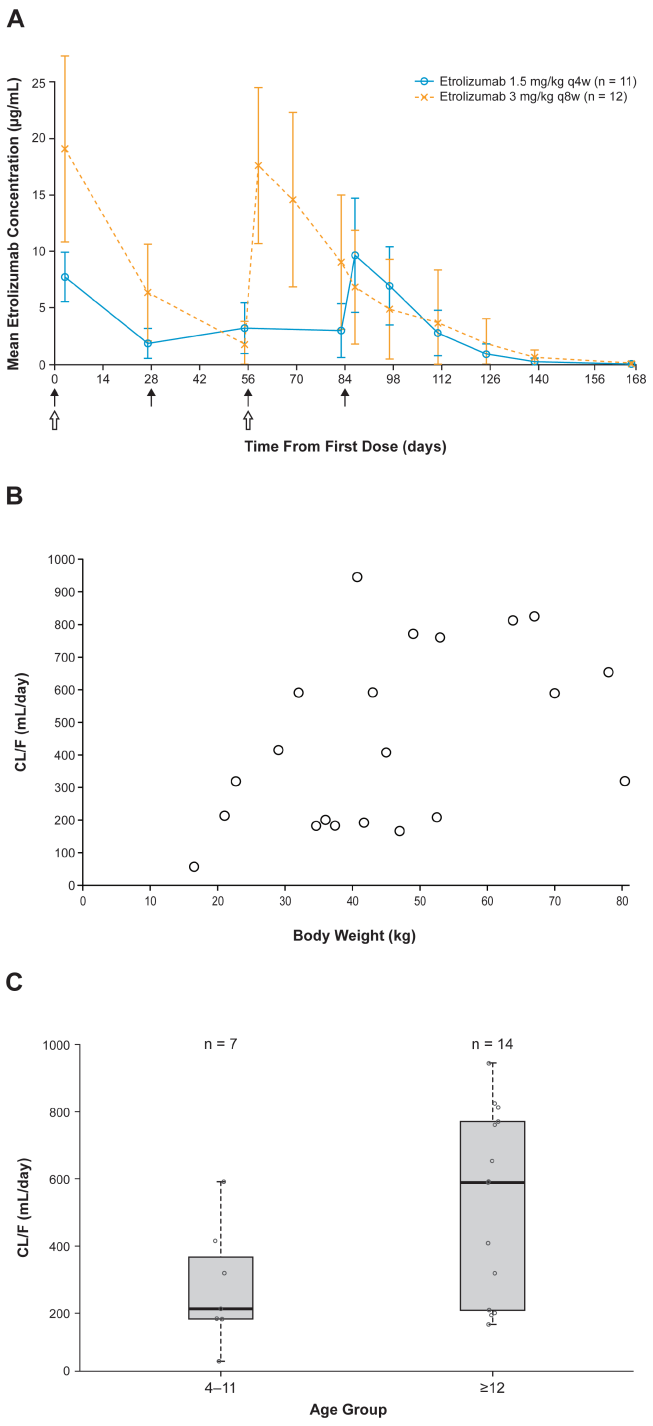

Figure 2. Etrolizumab pharmacokinetics. A, Arithmetic mean (±SD) serum concentration-time profiles of etrolizumab. Solid arrows indicate the time of subcutaneous dosing with etrolizumab 1.5 mg/kg q4w. Open arrows indicate the time of subcutaneous dosing with etrolizumab 3.0 mg/kg q8w. B, Relationship between etrolizumab clearance and body weight. C, Relationship between etrolizumab clearance and age group. Abbreviations: CL, clearance; F, bioavailability; q4w, every 4 weeks; q8w, every 8 weeks; SD, standard deviation.

efficacy assessment period). This reduction of β7 receptor occupancy continued through week 24 (day 168); however, the return of free $\beta7^{high}$ gut-homing T and B cell subsets to baseline levels was not yet reached before the end of the 8-week safety follow-up period.

Pharmacokinetic/Pharmacodynamic Relationship

Correlations between serum etrolizumab concentration and occupancy of β7 integrin receptors on peripheral blood $\beta7^{high}$ gut-homing CD4 T cells were evaluated. The results suggest that serum etrolizumab concentrations in the range of 1 µg/mL to 3 µg/mL or greater would be necessary to maintain complete to near-complete occupancy of β7 receptors in the pediatric population (Figure 3B). No notable differences in the pharmacokinetic/pharmacodynamic relationship were observed between different age groups and body weight groups.

Exploratory Biomarker Analyses

The exploratory biomarker assessment of soluble MAdCAM-1 (sMAdCAM-1) included all 24 patients who received at least 1 dose of etrolizumab. At baseline, the median serum levels of sMAdCAM-1 were similar between both dose groups. Following etrolizumab administration, median serum levels of sMAdCAM-1 decreased to similar levels in both dose groups (Figure S2), with the maximal decrease observed at week 12 (day 84) postdose (1.5 mg/kg q4w, 24.7% of baseline; 3.0 mg/kg q8w, 21.9% of baseline). This maximal decrease of sMAdCAM-1 was maintained in both dose groups throughout the etrolizumab dosing period. Serum levels of sMAdCAM-1 began to return toward baseline levels as observed at day 112 (4 weeks after the last dose of etrolizumab) in the 3.0 mg/kg q8w dose group and at day 126 (8 weeks after the last dose of etrolizumab) in the 1.5 mg/kg q4w dose group. The levels of sMAdCAM-1 returned close to baseline levels by week 24 (day 168) in both dose groups.

Safety

The median duration of etrolizumab exposure was 16.1 weeks for both dose groups, and the mean total cumulative dose of etrolizumab was 247.2 mg (107.76) in the 1.5 mg/kg q4w dose group and 270.6 mg (118.21) in the 3.0 mg/kg q8w dose group. The incidence of any-grade adverse events was comparable between groups (Table 3). In the 1.5 mg/kg q4w group, the adverse events with the highest incidence (≥20%) by preferred term were anemia, pyrexia, and abdominal pain, in descending order. In the 3.0 mg/kg q8w group, the adverse events with the highest incidence (≥20%) by preferred term were exacerbation of Crohn's disease and headache. A ≥25% difference in frequency between etrolizumab 1.5 mg/kg q4w and 3.0 mg/kg q8w was observed for pyrexia (33.3% [4 patients] vs 0%, respectively), anemia (33.3% [4 patients] vs 8.3% [1 patient], respectively), and headache (0% vs 25% [3 patients], respectively). Most adverse events were grade 1-2; 3 patients (25%) in each dose group had grade 3 adverse events (ie, diarrhea, exacerbation of ulcerative colitis, vomiting, anemia, anxiety disorder, exacerbation of Crohn's disease, varicella—each in 1 patient). Four of 24 patients (17%) experienced 7 serious adverse events (ie, diarrhea, gastritis, vomiting, anemia, anxiety disorder, exacerbation of ulcerative colitis, exacerbation of Crohn's disease—each in 1 patient). One serious adverse event (anxiety disorder) in the 1.5 mg/kg q4w dose group was reported by the investigator as related to treatment. Discontinuation from the study treatment because of serious adverse events was reported in 1 patient (8.3%) in the 1.5 mg/kg q4w dose group and 2 patients (16.7%) in the 3.0 mg/kg q8w dose group. No deaths, serious infections,

TABLE 2. Summary of mean pharmacokinetic parameters.

Parameter	Etrolizumab 1.5 mg/kg q4w (n = 11)	Etrolizumab 3.0 mg/kg q8w (n = 12)
C_{max}, µg/mL		
First dose	7.7 (2.18)	19.0 (8.21)
Last dose	9.8 (4.86)	18.1 (6.25)
AUC, µg · day/mL		
Days 56-112	—	521 (306)
Days 84-112	167 (86.9)	—
$t_{1/2}$, days	7.3 (1.76)	8.7 (3.74)
C_{trough}, µg/mL		
Day 28	1.8 (1.32)	—
Day 56	3.2 (2.24)	1.8 (1.99)
Day 84	3.0 (2.38)	—
Day 112*	2.8 (2.01)	3.7 (4.64)
CL/F, mL/day	505 (281)	385 (260)
Vz/F, mL	4920 (2440)	3910 (1830)

Data are mean (SD). Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum concentration; C_{trough}, trough concentration; q4w, every 4 weeks; q8w, every 8 weeks; SD, standard deviation; Vz/F, apparent volume of distribution during the terminal phase.
*Concentration after dosing.

opportunistic infections, malignancies, hypersensitivity reactions, or adverse events of special interest were reported.

Immunogenicity

The overall incidence of antidrug antibodies was 6 of 23 patients (26.1%), including 4 patients (36.4%) in the 1.5 mg/kg q4w dose group and 2 patients (16.7%) in the 3.0 mg/kg q8w dose group. For all patients testing positive for antidrug antibodies, onset time was 4 weeks.

Pharmacokinetic profiles for antidrug antibody–positive patients were similar to those of antidrug antibody–negative patients in the 1.5 mg/kg q4w dose group. In the 3.0 mg/kg q8w dose group, the 2 antidrug antibody–positive patients appeared to have lower exposure than the antidrug antibody–negative patients (Figure S3); however, the impact on pharmacokinetics was inconclusive because of the small sample size, given that other factors (such as age or body weight) may also impact etrolizumab exposure. Adverse events in antidrug antibody–positive patients were comparable with those in antidrug antibody–negative patients, and no adverse events of hypersensitivity or adverse events of special interest were reported in either group.

Exploratory Efficacy Analyses

All 24 patients in the intent-to-treat population were assessed for efficacy. At week 16, 6 of 10 patients (60%) with Crohn's disease experienced a clinical response based on the PCDAI; each dose group had 3 responders (Table 4). Among patients with ulcerative colitis, 9 of 14 patients (64.3%) experienced a clinical response based on the PUCAI at week 16: 5 responders were in the 1.5 mg/kg q4w dose group, and 4 responders were in the 3.0 mg/kg q8w dose group (Table 4).

No clinically meaningful changes in serum C-reactive protein levels or fecal calprotectin levels were observed from baseline to the end of the randomized study phase (week 16) in any of the patients enrolled or between dose groups (Table S1).

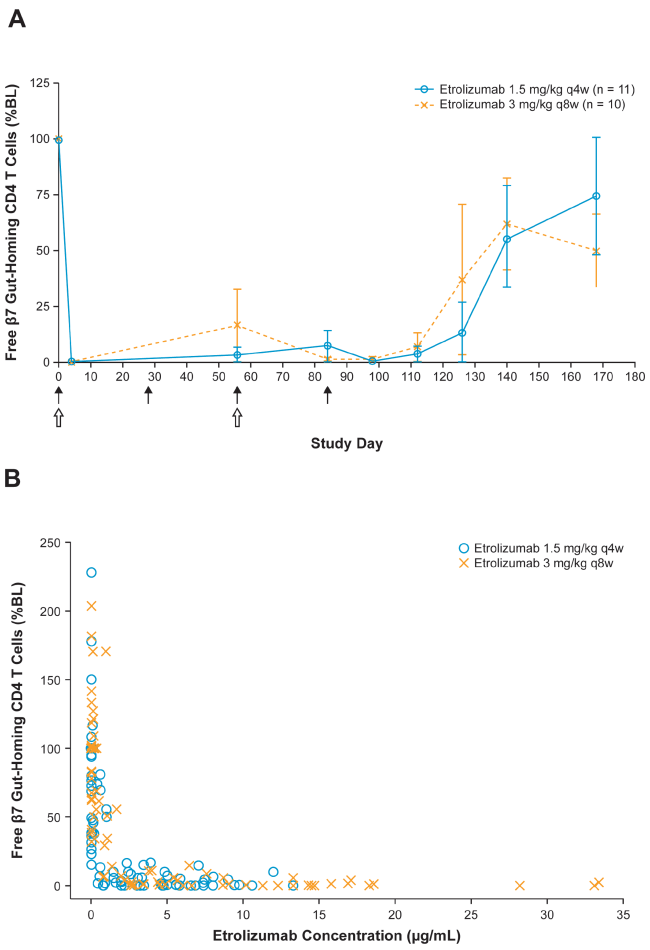

Figure 3. A, Median (±median absolute deviation) of absolute numbers of $\beta7^{high}$ gut-homing CD4 T cells with free β7 receptors expressed as a percentage of baseline. Solid arrows indicate the time of SC dosing with etrolizumab 1.5 mg/kg q4w. Open arrows indicate the time of SC dosing with etrolizumab 3.0 mg/kg q8w. B, Correlation between etrolizumab concentrations and absolute number of free $\beta7^{high}$ gut-homing CD4 T cells expressed as a percentage of baseline. Gut-homing CD4 T cells = $CD3^+CD4^+CD45RA^-\beta7^{high}$ T cells. Abbreviations: %BL, percent of baseline; q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous.

Discussion

One of the challenges in pediatric drug development is the lack of experimental data in pediatric populations that may inform dose selection for a first-in-children study. One frequently applied approach to overcome this limitation is the extrapolation of pharmacokinetics from adults. The doses in this phase 1 pharmacokinetic/pharmacodynamic study (1.5 mg/kg q4w and 3.0 mg/kg q8w) were selected based on exposure extrapolation from the adult population pharmacokinetic model. The dose of 1.5 mg/kg q4w was predicted to provide similar exposure to the 105 mg q4w dose used in phase 3 clinical trials in adult patients. The selection of the 3.0 mg/kg q8w dose was to evaluate pharmacokinetic dose proportionality and to allow for the characterization of the β7 receptor occupancy-time profile over a longer dose interval.

TABLE 3. Safety summary.

	Etrolizumab 1.5 mg/kg q4w (*n* = 12)	Etrolizumab 3.0 mg/kg q8w (*n* = 12)	All Patients (N = 24)
Any AE	9 (75.0%)	10 (83.3%)	19 (79.2%)
Any AE related to study treatment	1 (8.3%)	1 (8.3%)	2 (8.3%)
Any serious AE	2 (16.7%)	2 (16.7%)	4 (16.7%)
Any serious AE related to study treatment	1 (8.3%)	0	1 (4.2%)
Any AE leading to withdrawal from treatment	1 (8.3%)	2 (16.7%)	3 (12.5%)
Any AE leading to withdrawal related to study treatment	1 (8.3%)	0	1 (4.2%)

Data are number of patients with ≥1 event (% of patients). Adverse events reported as related to study treatment were determined by the investigator. Abbreviations: AE, adverse event; q4w, every 4 weeks; q8w, every 8 weeks.

TABLE 4. Clinical response at week 16.

	Etrolizumab 1.5 mg/kg q4w (*n* = 12)	Etrolizumab 3.0 mg/kg q8w (*n* = 12)	All patients (N = 24)
PCDAI			
N	5	5	10
Responder	3 (60.0)	3 (60.0)	6 (60.0)
Nonresponder	2 (40.0)	2 (40.0)	4 (40.0)
PUCAI			
N	7	7	14
Responder	5 (71.4)	4 (57.1)	9 (64.3)
Nonresponder	2 (28.6)	3 (42.9)	5 (35.7)

Data are number (%). Clinical response assessed for UC via PUCAI (defined as a decrease of at least 20 points) and for Crohn's disease via PCDAI (defined as a decrease of at least 15 points). Abbreviations: PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; q4w, every 4 weeks; q8w, every 8 weeks.

Etrolizumab showed linear pharmacokinetics in adults across doses ranging from 1 mg/kg to 10 mg/kg.[2] The results from this pediatric study showed that the observed C_{max} increased proportionally as dose increased. However, AUC_{tau} was slightly higher in the 3.0 mg/kg q8w dose group than in the 1.5 mg/kg q4w dose group after accounting for dosing interval differences. No formal dose proportionality analysis was performed because only 2 doses (with different dosing frequencies) were tested with a limited number of patients. Wider variability in the concentration-time profile was observed with the 3.0 mg/kg q8w dose, which may in part contribute to the higher than dose-proportional AUC from this group. The mean elimination half-life was 7.3 days and 8.7 days for the 1.5 mg/kg q4w and 3.0 mg/kg q8w dose groups, respectively, similar to what has been observed in adults. In a phase 1 study of adult patients, the mean half-life was 7.7 days and 10.1 days following subcutaneous administration of 1.5 mg/kg q4w and 3 mg/kg q4w, respectively.[11]

Adult population pharmacokinetic analysis has demonstrated body weight to be a significant covariate for clearance.[4] Here, the impact of body weight and age on clearance was explored in the pediatric population. As expected, etrolizumab clearance was correlated with body weight in children as well as in adults. It appeared that clearance was positively correlated with body weight for patients with a body weight of less than 35 kg; however, the correlation between clearance and body weight for patients with a body weight of greater than 35 kg was less clear because of the wide variability and small sample size. A similar trend was observed for the impact of age on clearance because body weight and age were correlated. The median clearance in patients age 4 to 11 years was lower than that in patients older than 12 years. Given the small sample size, large variability, and impact of other covariates on pharmacokinetics, further evaluation of the impact of body weight and age on clearance in the pediatric population is warranted. In addition, larger clinical studies are needed to elucidate potential effects of baseline disease severity, serum albumin levels, or other covariates on pharmacokinetic parameters in the pediatric population. Model-based analysis will be helpful to select appropriate doses in children across different age ranges and body weights.

Robust pharmacodynamic effects were achieved in both treatment groups, consistent with those observed in adult patients.[3,11,12] This includes the complete/near-complete occupancy of β7 receptors following etrolizumab treatment and the decrease of serum sMAdCAM-1 by way of inhibiting β7-MAdCAM-1 interactions and resultant cellular homing. Results of β7 receptor occupancy analyses showed that in both treatment groups, median numbers of free $\beta7^{high}$ gut-homing CD3 T cells, CD4 T cells, CD8 T cells, and CD19 B cells declined to below 10% of baseline, confirming etrolizumab target engagement in the pediatric population and indicating complete/near-complete occupancy of β7 receptors at the dose levels evaluated. Furthermore, the maintenance of complete β7 receptor occupancy in peripheral blood and the observed maximal decrease in serum levels of sMAdCAM-1 further add to the evidence that maximal pharmacodynamic effects were achieved in these pediatric patients. The pharmacokinetic/pharmacodynamic relationship identified between serum etrolizumab concentrations and β7 receptor occupancy indicated that concentrations in the range of 1 μg/mL to 3 μg/mL or greater would be required to maintain complete/near-complete occupancy of β7 receptors in children with inflammatory bowel disease, which is consistent with the observations from adult phase 1 and phase 2 studies.[12] Receptor occupancy was primarily concentration-driven and did not appear to be weight- or age-dependent. These data are important to inform dosing regimens in any future pediatric studies with etrolizumab.

Of note, there is some evidence that increasing the dose of anti-integrin therapies (eg, vedolizumab) beyond full β7 receptor occupancy may provide additional therapeutic benefit in patients with inflammatory bowel disease.[13,14] Although the mechanisms for this are not fully understood, recent studies suggest that maintaining higher serum trough levels may be

associated with alterations in innate immunity.[15] Therefore, the exposure-efficacy relationship identified in adult data, in addition to β7 receptor saturation, will play an important role in identifying the appropriate dosing regimen for the pediatric population.

Results of exploratory efficacy analyses showed that approximately 60% of patients with ulcerative colitis or Crohn's disease achieved a clinical response, which is higher than previously documented clinical response rates in adults with inflammatory bowel disease receiving etrolizumab. It is important to note that this was an open-label study and that patients, caregivers, and investigators were aware of the dosing regimen used. Although the impact of open-label dosing on efficacy assessments is unclear, this study design might have resulted in an overestimation of symptomatic benefit. This study was not powered to demonstrate etrolizumab efficacy, and any exposure-response relationship could not be appropriately evaluated in this phase 1 study because of the small sample size.

Inflammatory biomarkers such as serum C-reactive protein and fecal calprotectin did not demonstrate clinically meaningful changes in this study, possibly because of the small sample size and/or short duration of etrolizumab treatment. However, this study was not focused on efficacy or treatment effect, and efficacy measures did not include an endoscopy component. Large randomized controlled trials designed to assess efficacy are needed to validate the current findings for etrolizumab in pediatric patients with inflammatory bowel disease.

The incidence of positive antidrug antibody tests in the pediatric population was comparable with that in the adult population in the etrolizumab phase 3 ulcerative colitis studies.[16–19] Because the rate of adverse events in antidrug antibody–positive patients was similar to that in antidrug antibody–negative patients, it appeared that antidrug antibodies did not have an impact on safety. The pharmacokinetics of antidrug antibody–positive patients in the 1.5 mg/kg q4w dose group appeared to be similar to those of antidrug antibody–negative patients (Figure S3a). In the 3.0 mg/kg q8w dose group, there were 2 patients who tested positive for antidrug antibodies. Although the overall pharmacokinetic exposures in these 2 patients were relatively low, their pharmacokinetic profiles did not show apparent exposure changes after the onset of antidrug antibody formation at week 4, indicating that the lower exposure in these 2 patients might not have resulted from the formation of antidrug antibodies (Figure S3b). In the phase 3 studies of adult patients with ulcerative colitis, no obvious impact of antidrug antibodies on pharmacokinetic outcomes was observed. Given these adult data and results from this pediatric study, the likelihood that antidrug antibodies impacted pharmacokinetics in the pediatric population is relatively low.

Overall, the majority of adverse events reported in this study were grade 1-2. The adverse events reported were consistent with the current safety profile of etrolizumab in adults.[3,11] No adverse events of special interest were observed, and no new safety signals emerged.

Conclusion

In conclusion, the pharmacokinetics and pharmacodynamics of etrolizumab were characterized in children with moderately to severely active inflammatory bowel disease. Two major covariates that impacted clearance and exposure were body weight and age. The exposure needed to maintain complete/near-complete occupancy of β7 receptors was similar between adults and children. Etrolizumab also demonstrated clinical activity as assessed by disease activity indices, though endoscopy was not performed. The safety and tolerability in pediatric patients were consistent with the current safety profile of etrolizumab in adults.

Supplementary data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Author Contributions

W.Z. contributed to study design and conception, data analysis, and manuscript writing; A.S. contributed to study design and conception, data analysis, and manuscript writing; F.F. contributed to study design and conception, data analysis, and manuscript writing; J.M. contributed to study design and conception, data analysis, and manuscript writing; G.S. contributed to data analysis, study validation, and manuscript writing; J.K. contributed to study conception, study conduct, and manuscript writing; B.K. contributed to study conception, study conduct, and manuscript writing; R.L. contributed to study design and conception, data analysis, and manuscript writing; M.A. contributed to study design and conception, data analysis, and manuscript writing; A.K. contributed to study design and manuscript writing; KT.P. contributed to study design and manuscript writing; M.T.T. contributed to study design and conception, data analysis, and manuscript writing. W.Z. and A.S. contributed equally to this article. All authors have reviewed and approved the manuscript and have contributed significantly to the work.

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Conflicts of Interest

W.Z., F.F., J.M., G.S., M.A., and KT.P. are employees of Genentech, Inc. and receive salary and stock options. A.S. and R.L. are employees of Roche Products Limited and receive salary and stock options. J.K. and B.K. received grants from Hoffmann-La Roche during the conduct of the study. A.K. and M.T.T. were employees of Genentech, Inc. during the conduct of the study.

Data Availability

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for

eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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