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Gastroenterology: Inflammatory Bowel Disease

Ustekinumab in paediatric patients with moderately to severely active Crohn's disease: UniStar study long-term extension results

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Abstract

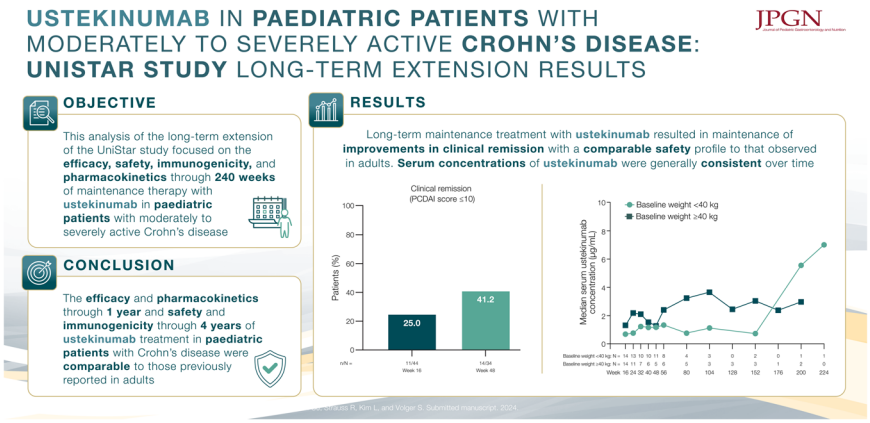
Objectives: To assess the efficacy, safety, immunogenicity, and pharmacokinetics through 240 weeks of ustekinumab treatment in paediatric patients from the long-term extension (LTE) of the phase 1, double-blind UniStar trial.

Methods: Paediatric patients with moderately to severely active Crohn's disease (CD) were randomised 1:1 and stratified by body weight (<40 or ≥40 kg) to low- or high-dose intravenous ustekinumab followed by a subcutaneous maintenance dose at Week 8. At Week 16, patients were eligible to enter the LTE at the discretion of the investigator and continued maintenance dosing every 8 weeks up to Week 240.

Results: Of the 34 patients who entered the LTE, 25 patients with evaluable data completed Week 48, and 41.2% (14/34) achieved clinical remission at Week 48. Among the 24 patients with Week-0 C-reactive protein (CRP) levels ≥3 mg/L, 29.2% (7/24) achieved normalisation of CRP at Week 48, while imputing missing data as failures. Through Week 240, the most common adverse events were infections ($n = 28$) and gastrointestinal disorders ($n = 26$). The most common serious adverse event was worsening of CD ($n = 6$). Only one patient had detectable antibodies to ustekinumab. Median serum ustekinumab concentrations remained consistent through Week 48, were detectable through Week 224, and trended lower in patients <40 kg.

Registration: ClinicalTrials.gov Identifier: NCT02968108 (http://classic.clinicaltrials.gov/ct2/show/results/NCT02968108).

Conclusions: Efficacy and pharmacokinetics through 1 year and safety and immunogenicity through 4 years of ustekinumab treatment in paediatric patients with CD were generally comparable to those previously reported in adults.



KEYWORDS
biologics, Crohn's disease (CD), inflammatory bowel disease (IBD), paediatric gastroenterology

1 | INTRODUCTION

Crohn's disease (CD) is characterised by chronic inflammation and a potentially complicated disease course, which may include surgical resections.[1,2] Treatment options for paediatric patients with CD are limited.[3] Often adverse effects and loss of response preclude continued use of corticosteroids and immunomodulators.[1,3] Although tumour necrosis factor (TNF) antagonists are recommended for paediatric patients with CD,[3,4] infliximab and adalimumab are the only approved biologic agents.[5]

Ustekinumab is a fully human immunoglobulin G1κ monoclonal antibody that binds the p40 subunit of interleukin-12 and -23 and was approved in 2016 for the treatment of adults with moderately to severely active CD.[5,6] In adults with treatment failure or intolerance to TNF antagonists or conventional therapies, ustekinumab induction led to clinical response and remission of CD[7] that was sustained through 5 years of maintenance therapy.[8–10]

The phase 1 UniStar study evaluated the efficacy, safety, immunogenicity, and pharmacokinetics of ustekinumab in paediatric patients with moderately to severely active CD.[11] Through 16 weeks of ustekinumab treatment, 52.3% (23/44) of patients achieved clinical response. A favourable safety profile, and no antibodies to ustekinumab were detected, similar to results observed in adult patients in the phase 3 ustekinumab studies.[7,11] Here, we report results of the long-term extension (LTE) of the UniStar study through 240 weeks of maintenance therapy with ustekinumab.

What is Known

- The UniStar 16-week induction study reported ustekinumab concentrations in paediatric patients with Crohn's disease (CD) and body weight ≥40 kg were comparable to adults with CD; patients <40 kg may require a different dosing regimen.
- Efficacy, pharmacokinetics (PK), safety, and immunogenicity of ustekinumab were similar between paediatric and adults with CD.

What is New

- In the long-term UniStar extension, 41.2% (14/34) of patients who continued ustekinumab maintained remission at Week 48.
- Efficacy and PK through 1 year in ustekinumab-treated paediatric patients were comparable to those previously reported in adults. No new safety or immunogenicity signals were reported through 4 years of ustekinumab treatment.

2 | METHODS

2.1 | Study design of UniStar LTE

The UniStar LTE was the extension period of the UniStar study (ClinicalTrials.gov Identifier: NCT02968108), an

international, multicentre, randomised, double-blind, pharmacokinetic study of intravenous (IV) ustekinumab induction followed by subcutaneous (SC) ustekinumab maintenance in paediatric patients with moderately to severely active CD.[11] Patients were randomised 1:1 and stratified by body weight (<40 or ≥40 kg) to receive a single induction dose of lower- or higher-dose IV ustekinumab (lower dose: 3 mg/kg [<40 kg] and 130 mg [≥40 kg]; higher dose: 9 mg/kg [<40 kg] and 390 mg [≥40 kg]). Doses specified as higher were selected to deliver ustekinumab exposure comparable to a reference adult population with CD.[7,12] At Week 8, patients received a single SC maintenance dose of ustekinumab (2 mg/kg [<40 kg]; 90 mg [≥40 kg]). At Week 16, eligible patients who in the opinion of the investigator, responded to ustekinumab treatment (improvement in clinical symptoms with no significant adverse event or worsening disease, etc.) entered the LTE and continued SC ustekinumab maintenance dosing (2 mg/kg [<40 kg]; 90 mg [≥40 kg]) every 8 weeks up to Week 240 (Supporting Information: Figure 1). Patients who lost response to ustekinumab treatment were not given the option to dose adjust. However, CD–specific therapies were allowed at the discretion of the investigator.

After completion of the LTE, patients who were <18 years old and, in the opinion of the investigator, the parent, and the patient were still receiving benefit from ustekinumab (improvement in clinical symptoms with no significant adverse event or worsening disease, etc.), were eligible to enter the UNITED basket LTE study (ClinicalTrials.gov Identifier: NCT05092269). The end of the UniStar LTE study was defined as the time when the last patient had either completed the Week-240 visit or upon availability of the UNITED LTE study, whichever occurred first, or when patients had completed the final safety visit, approximately 20 weeks after last study dose. The last ustekinumab dose was administered at Week 240.

2.2 | Patient population

The full inclusion and exclusion criteria for UniStar were described previously.[11] Briefly, at baseline, patients were 2 to <18 years old (United States) or 6 to <18 years old (Canada and Europe) with body weight ≥10 kg, and Paediatric Crohn's Disease Activity Index (PCDAI) score of >30, with ≥1 of the following: a C-reactive protein (CRP) value of >3 mg/L, faecal calprotectin of >250 mg/kg, or an ileocolonoscopy with evidence of active CD (Supporting Information: Methods).

2.3 | Efficacy evaluations

Clinical efficacy and inflammatory biomarkers were evaluated from enrolment in the LTE period (Week 16 of UniStar) through Week 224. The PCDAI was used to evaluate clinical remission (PCDAI score ≤10 points), which was assessed every 8 weeks from Weeks 24 to 48, and every 24 weeks from Week 56 through the end of the study (Supporting Information: Methods). Blood samples for evaluation of CRP were collected every 8 weeks from Week 24 to 48 and thereafter approximately every 24 weeks. Stool faecal calprotectin and lactoferrin was tested every 24 weeks from Week 24.

The IMPACT-III questionnaire, a validated patient-report measure of health-related quality of life in paediatric (≥10 years old) and adolescent inflammatory bowel disease, was collected at Week 48 (Supporting Information: Methods).

2.4 | Safety evaluations

Safety and tolerability of ustekinumab were assessed at every study visit. Patients who did not enter the UNITED LTE had the final safety follow-up visit 20 weeks after last administration of ustekinumab. Patients who transitioned directly to commercial ustekinumab had a final safety visit prior the first dose of commercial product. Adverse events (AEs), including serious AEs (SAEs) and AEs leading to discontinuation of ustekinumab, were summarised by type and frequency. Possible anaphylaxis and delayed hypersensitivity reactions were also recorded. Treatment-emergent AEs were coded in accordance with the *Medical Dictionary for Regulatory Activities* (MedDRA®), version 24.1.

2.5 | Immunogenicity and pharmacokinetic evaluations

Blood serum ustekinumab concentration and antibodies were measured every 8 weeks through Week 56, every 24 weeks thereafter, and at early termination and safety follow-up visits (Supporting Information: Methods).

2.6 | Statistical analysis

No formal hypothesis testing was conducted. All patients who received one or more administrations of ustekinumab during the LTE were included in the analyses. Descriptive statistics (e.g., mean, standard deviation [SD], median, interquartile range [IQR], minimum and maximum) were used to summarise continuous variables. Counts and percentages were used to summarise categorical variables. For efficacy analyses, treatment failure rules were applied to nonmissing data (baseline observation carried forward for continuous data and nonresponder/remitters

imputation [NRI] for dichotomous data). All missing data were left as missing, with the exception of post hoc analyses of selected Week- 48 clinical efficacy endpoints, for which missing data were imputed (last observation carried forward for continuous data and NRI for dichotomous data). Efficacy data beyond Week 48 were limited as patients were able to transition to commercial product (where available) or enter the UNITED LTE study at varying timepoints.

2.7 | Ethics

The study was conducted in accordance with the Declaration of Helsinki and consistent with Good Clinical Practice. Study protocols were reviewed and approved by an Independent Ethics Committee or Institutional Review Board. Patients or their legally acceptable representatives provided written informed consent.

3 | RESULTS

3.1 | Patients

All 34 patients received at least one administration of ustekinumab during the LTE and were included in efficacy and safety analyses; the study began 24 January 2017 (first patient signed informed consent) and completed 18 March 2022 (last observation for last patient recorded). Of the 34 patients in the LTE, 61.8% (21/34) were female with a median (IQR) age of 13.0 (12.0–16.0) years (Table 1). At enrolment in UniStar (baseline Week 0), median (IQR) CD duration was 3.6 (2.1–6.6) years and median (IQR) PCDAI score was 42.5 (37.5–50.0). Most patients had abnormal baseline levels of inflammatory markers at Week 0, the start of UniStar (CRP ≥ 3 mg/L: 70.6%; faecal calprotectin >250 mg/kg: 85.3%; faecal lactoferrin >7.24 µg/g: 97.1%; Table 1).

At the start of the LTE, 50.0% of patients reported receiving ≥1 concomitant medications. Oral corticosteroids (14.7%, 5/34), 6-mercaptopurine and/or azathioprine (11.8%, 4/34) and antibiotics (11.8%, 4/34) were the most frequently used medications. Most patients had a history of immunomodulator (91.2%, 31/34) and/or corticosteroid (58.8%, 20/34) treatment failure, and at least one anti-TNF failure (94.1%, 32/34) (Table 1).

From enrolment in the LTE through Week 48, 23.5% (8/34) of patients discontinued ustekinumab treatment, of which 5.9% (2/34) discontinued due to an AE. Through the final safety visit at Week 240, 76.5% (26/34) of patients (Figure 1) discontinued ustekinumab treatment due to: lack of efficacy and/or worsening of CD ($n = 14$), patient withdrawal ($n = 7$), reasons recorded as 'other' ($n = 3$), CD–related surgery ($n = 1$), or patient declining further treatment ($n = 1$).

Based on the post hoc analysis of all patients who enroled in the LTE, 38.2% (13/34) of the patients were in corticosteroid-free clinical remission at Week 48; 90.0% (9/10) of the patients who were in clinical remission at Week 8 were still in clinical remission at Week 48.

3.2 | Efficacy at 1 year

At Week 48, after approximately 1 year of ustekinumab treatment, 41.2% (14/34) of patients achieved PCDAI clinical remission (Figure 2). Of those who were previously in clinical remission at Week 8 (after IV induction dose), 90.0% (9/10) remained in remission at Week 48. Overall, 38.2% (13/34) of patients achieved corticosteroid-free clinical remission at Week 48. Among the patients who remained in the study, the proportion in clinical remission remained high throughout the LTE (Supporting Information: Table 1).

At Week 48, of the 17 patients with abnormal CRP values at Week 0 and available CRP data at Week 48, 41.2% (7/17) achieved normalisation of CRP (Supporting Information: Figure 2). Assuming that patients with missing data did not achieve CRP normalisation, among the 24 patients with abnormal CRP values at Week 0, 29.2% (7/24) achieved normalisation of CRP at Week 48. Among patients with abnormal values at Week 0 and available data at Week 48, 36.8% (7/19) achieved normalisation of faecal calprotectin (Supporting Information: Figure 3), and 30.0% (6/20) achieved normalisation of faecal lactoferrin at Week 48 (Supporting Information: Figure 4). The proportion of patients achieving normalisation of these inflammatory markers generally remained high throughout the LTE, although the number of patients remaining in the study decreased after Week 48.

The mean (SD) IMPACT-III score at Week 0 was 107.9 (17.2). At Week 48, patients reported an improvement in health-related quality of life, with a mean (SD) IMPACT-III score of 131.1 (22.8) and a mean (SD) change from baseline of 23.9 (25.4).

3.3 | Safety and immunogenicity

Safety events for the first 16 weeks of ustekinumab treatment in UniStar were described previously.[11]

3.3.1 | Safety events through 1 year of follow up (Week 0 through Week 48)

Throughout the first year of ustekinumab treatment (mean follow-up duration of 45.1 weeks), 88.2%

TABLE 1 Demographic and disease characteristics at baseline (Week 0) of the long term extension (LTE) period.

Demographic/ characteristic	Low dose induction: 3 mg/ kg IV[a] or 130 mg IV[b] (*N* = 18)	High dose induction: 9 mg/ kg IV[a] or 390 mg IV[b] (*N* = 16)	Combined (*N* = 34)
Age (years), median (IQR)	13.0 (11.0–15.0)	14.0 (12.0–16.0)	13.0 (12.0–16.0)
Sex (female)	14 (77.8)	7 (43.8)	21 (61.8)
Body weight (kg), median (IQR)	38.8 (34.3–53.7)	42.2 (28.6–50.3)	41.1 (33.0–50.5)
<40 kg	10 (55.6)	6 (37.5)	16 (47.1)
≥40 kg	8 (44.4)	10 (62.5)	18 (52.9)
CD disease duration (years), median (IQR)	3.3 (1.9–5.4)	4.7 (2.3–8.4)	3.6 (2.1–6.6)
PCDAI[c]			
PCDAI score, median (IQR)	42.5 (37.5–51.3)	42.5 (36.3–48.8)	42.5 (37.5–50.0)
Remission or mild disease (PCDAI score ≤30)	2 (12.5)	3 (18.8)	5 (15.6)
Moderate disease (PCDAI score >30 to ≤40)	4 (25.0)	4 (25.0)	8 (25.0)
Severe disease (PCDAI score >40)	10 (62.5)	9 (56.3)	19 (59.4)
SES-CD, median (IQR)	16.0 (6.0–23.0)	14.0 (11.0–18.0)	14.0 (8.0–23.0)
Involved GI areas[c]			
Ileum only	2 (11.1)	1 (6.7)	3 (9.1)
Colon only	6 (33.3)	4 (26.7)	10 (30.3)
Ileum and colon	10 (55.6)	10 (66.7)	20 (60.6)
CRP (mg/L), median (IQR)	11.6 (2.5–19.9)	6.8 (2.2–20.3)	10.4 (2.4–19.9)
Abnormal CRP (≥3 mg/L)	13 (72.2)	11 (68.8)	24 (70.6)
Faecal calprotectin (mg/ kg), median (IQR)	2510 (550–5570)	1665 (759–2865)	2026 (710–3796)
Abnormal faecal calprotectin (>250 mg/kg)	16 (88.9)	13 (81.3)	29 (85.3)
Faecal lactoferrin (μg/g), median (IQR)	193.6 (34.3–271.6)	135.7 (70.4–396.8)	163.5 (63.0–290.9)
Abnormal faecal lactoferrin (>7.24 μg/g)	17 (94.4)	16 (100.0)	33 (97.1)
Concomitant CD medications	10 (55.6)	7 (43.8)	17 (50.0)
6-mercaptopurine/ azathioprine	2 (11.1)	2 (12.5)	4 (11.8)
Methotrexate	2 (11.1)	1 (6.3)	3 (8.8)
Oral aminosalicylates	0	1 (6.3)	1 (2.9)

(Continues)

TABLE 1 (Continued)

Demographic/ characteristic	Low dose induction: 3 mg/ kg IV[a] or 130 mg IV[b] (*N* = 18)	High dose induction: 9 mg/ kg IV[a] or 390 mg IV[b] (*N* = 16)	Combined (*N* = 34)
Antibiotics	4 (22.2)	0	4 (11.8)
Oral corticosteroids	2 (11.1)	3 (18.8)	5 (14.7)
Prior anti–TNF treatment failure	17 (94.4)	15 (93.8)	32 (94.1)
Infliximab	14 (77.8)	13 (81.3)	27 (79.4)
Adalimumab	10 (55.6)	9 (56.3)	19 (55.9)
Certolizumab pegol	0	0	0
Prior corticosteroid treatment failure	13 (72.2)	7 (43.8)	20 (58.8)
Prior immunomodulator treatment failure	16 (88.9)	15 (93.8)	31 (91.2)

Note: Data are *n* (%) unless otherwise indicated.

Abbreviations: CD, Crohn's disease; CRP, C-reactive protein; GI, gastrointestinal; IQR, interquartile range; IV, intravenous; LTE, long-term extension; PCDAI, Paediatric Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumour necrosis factor.

[a]For baseline body weight <40 kg.

[b]For baseline body weight ≥40 kg.

[c]Sixteen patients per group had available PCDAI data (combined *n* = 32); 1 patient in the high-dose induction group did not have reported involved GI area (combined *n* = 33). The ileocolonoscopy was done and read centrally, and the SES-CD was computed to assess mucosal inflammation.

(*n* = 30) of patients experienced ≥1 AE and 14.7% (*n* = 5) experienced SAEs. Infections were reported in 67.6% (*n* = 23) of patients. During this time, 5.9% (*n* = 2) of patients discontinued ustekinumab treatment due to an AE.

3.3.2 | Safety events in the LTE period (enrolment through Week 240)

From enrolment through the final safety follow-up visit at Week 240, the mean (SD) duration of follow-up was 103.5 (76.1) weeks, with a mean (SD) of 13.2 (9.7) ustekinumab administrations. Key safety findings from the LTE are summarised in Table 2 and were generally similar to those observed in the overall study.

3.3.3 | Safety events in the entire study period (Week 0 through Week 240)

Throughout the UniStar study, 94.1% (*n* = 32) of patients experienced ≥1 AE (Supporting Information: Table 2). The most commonly reported AEs were infections (82.4%, *n* = 28), including nasopharyngitis (32.4%, *n* = 11) and upper respiratory tract infection (29.4%, *n* = 10). Gastrointestinal (GI) disorders were common (76.5%, *n* = 26), with worsening of CD the most frequently reported (41.2%, *n* = 14), followed by vomiting (23.5%, *n* = 8) and abdominal pain (20.6%, *n* = 7). Other common AEs included headache (38.2%, *n* = 13), pyrexia (23.5%, *n* = 8), and fatigue (20.6%, *n* = 7).

Among the 11 (32.4%) patients who experienced ≥1 SAE, the most commonly reported was worsening of CD (17.6%, *n* = 6; 1 of these events was considered reasonably related to ustekinumab); 1 SAE each of anal ulcer, constipation, large intestinal stenosis, pancreatitis, and vomiting were reported. Non-GI SAEs were singular events (*n* = 1 each) of pyrexia, malnutrition, syncope, and appendicitis.

Throughout the study, no injection-site reactions, possible anaphylactic or delayed hypersensitivity reactions, malignancies, or deaths were reported.

Incidence of ustekinumab antibodies was low, occurring in one patient randomised to the lower induction dose, with a peak titre of 1:100. This patient was also positive for neutralising antibodies.

3.4 | Pharmacokinetics

Median serum ustekinumab concentrations were generally consistent from enrolment through the final safety follow-up visit at Week 224, trending lower in patients with body weight <40 kg, regardless of ustekinumab dose (Figure 3; Supporting Information: Table 3). Serum ustekinumab levels were detectable through Week 200; however, a small number of patients remained in the study at this time point. No relationships between clinical

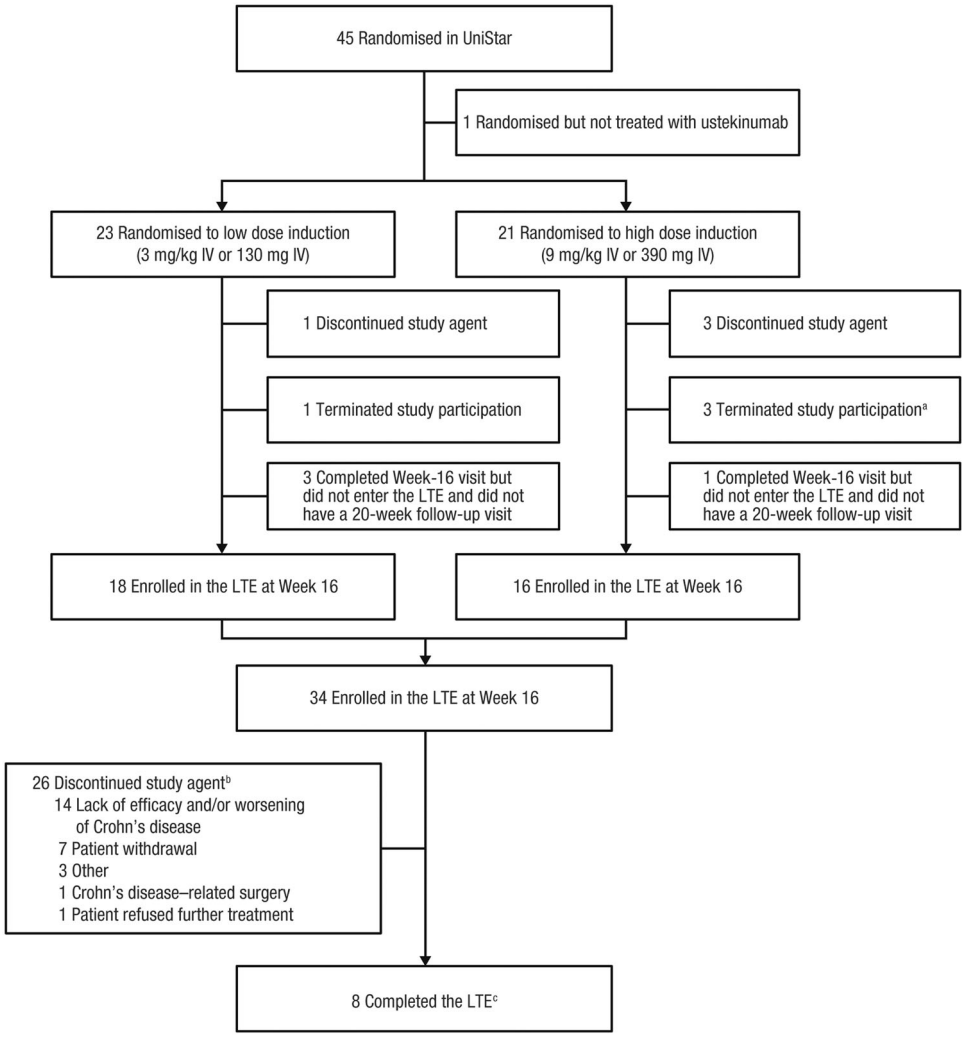


FIGURE 1 Patient disposition. [a]Includes two patients who discontinued study agent. [b]Two patients who had transitioned to the UNITED basket study were incorrectly captured as discontinuing study agent (reason listed as 'other') and are not shown. [c]Received ustekinumab at Week 208.

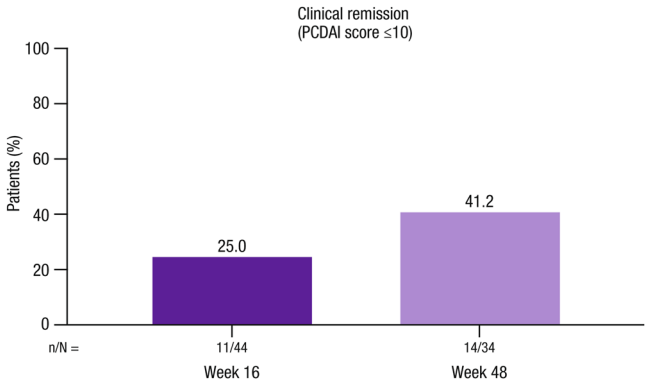


FIGURE 2 Clinical remission at Weeks 16 and 48. *N*, number of patients with available data; PCDAI, Paediatric Crohn's Disease Activity Index.

efficacy outcomes and serum ustekinumab concentrations were observed at Week 48, likely due to the small number of patients in the study.

4 | DISCUSSION

Among paediatric patients with CD benefiting at Week 16 following induction, long-term maintenance treatment with ustekinumab resulted in continued improvements in clinical remission and sustained decreases in inflammatory biomarker levels. Overall, ustekinumab therapy was well-tolerated in paediatric patients, with a safety profile generally consistent with that observed in an adult population,[7] with a low incidence of ustekinumab antibodies.

Ustekinumab treatment through Week 16 was previously shown to provide meaningful improvements from baseline in PCDAI-based clinical efficacy evaluations.[11] Long-term maintenance therapy resulted in further improvements in clinical remission at 1 year, reflected in an improvement in IMPACT III–based health-related quality of life at Week 48. The proportion of paediatric patients achieving clinical remission (41.2%) at Week 48 was consistent with outcomes observed in the anti-TNF failure subgroup in an adult study[7] in which 41.1% of patients receiving maintenance ustekinumab every 8 weeks achieved CDAI-based clinical remission at Week 44. Long-term maintenance therapy also led to decreases from baseline in inflammatory biomarker levels, including CRP, faecal calprotectin, and faecal lactoferrin. The proportion of paediatric patients achieving normalisation of faecal calprotectin (36.8%) at Week 48 was consistent with that observed in an adult population (30.1%) at Week 44.[7] Decreases in inflammatory biomarkers evaluated in this study persisted through approximately 4 years of treatment.

TABLE 2 Safety events from enrolment in the LTE through the final safety follow-up visit at Week 240.

Safety event	Patients in the LTE (*N* = 34)
Mean (SD) duration of follow-up (weeks)	103.5 (76.1)
Mean (SD) exposure, number of administrations	13.2 (9.7)
Patients with ≥1	
Adverse event	31 (91.2)
Serious adverse event	11 (32.4)
Infections[a]	25 (73.5)
COVID-19 infections	1 (2.9)
Serious infections[a]	0
Malignancies	0
Discontinued study agent due to ≥1 adverse event	5 (14.7)
Deaths	0
Injection site reactions	0
Possible anaphylactic reactions or delayed hypersensitivity (serum sickness–like) reactions	0
Antibodies to ustekinumab	1 (2.9)

Note: Data are *n* (%) unless otherwise indicated.

Abbreviations: COVID-19, coronavirus disease; LTE, long-term extension; SD, standard deviation.

[a]Infection as assessed by the investigator.

The safety profile through 4 years of ustekinumab treatment in paediatric patients was generally consistent with that observed during the first 16 weeks of treatment[11] and with adult patients receiving ustekinumab.[7,12] No serious infections, opportunistic infections including tuberculosis, malignancies, or deaths were reported. SAEs were reported in 32.4% of patients from Week 16 through Week 240, with 11.8% occurring from Week 16 through 1 year of follow-up. The majority of SAEs were related to complications commonly associated with CD, including worsening CD, anal ulcers, large intestinal stenosis, malnutrition, and vomiting. Additionally, the proportion of SAEs in the present study was consistent with those reported in other clinical trials of biologic treatment in paediatric CD. In a study of infliximab maintenance in children with CD, a total of 19.6% of patients receiving IV infliximab induction and/or every 8 or 12 weeks reported SAEs through 54 weeks of treatment.[13] Similarly, SAEs were reported in 23.7% and 47.9% of paediatric patients receiving SC adalimumab 20 or 40 mg/kg every other

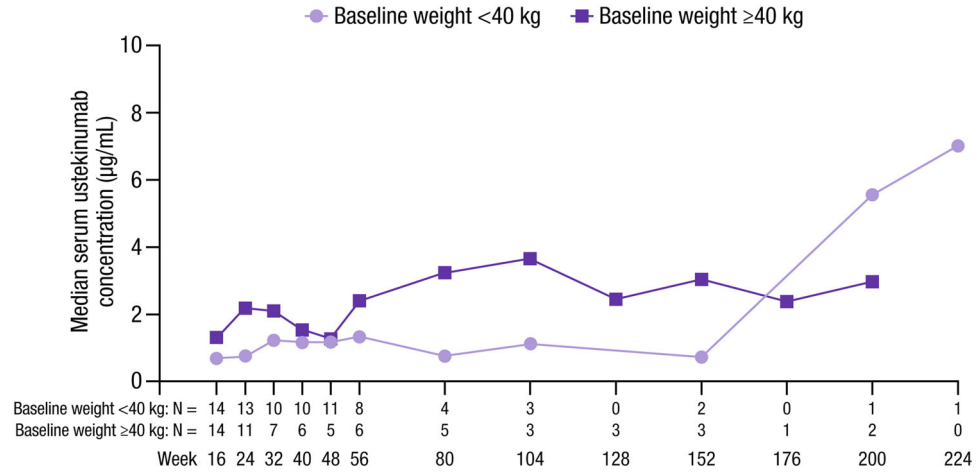


FIGURE 3 Median serum concentration of ustekinumab from enrolment in the LTE through Week 224, stratified by body weight at baseline. LTE, long-term extension; *N*, number of patients with available data.

week (or weekly dosing from Week 12 for patients with disease flare or nonresponse) up to Week 52[14] and through 5 years, respectively.[15] In the UniStar study, at enrolment, no patients had developed antibodies to ustekinumab,[11] and throughout the LTE only one patient had detectable antibodies, indicating that the overall immunogenicity profiles are similar to those observed in adults.[12]

Previous results from the initial induction and maintenance periods (through Week 16) of the UniStar study[11] showed that serum concentrations of ustekinumab in paediatric patients with CD were generally consistent with those observed in a reference adult population,[12] but lower in children with body weight <40 kg. Through Week 48 of the LTE, serum ustekinumab concentrations were similar to those observed during the first 16 weeks of treatment.[11] Although ustekinumab concentrations tended to be lower in paediatric patients <40 kg versus ≥40 kg, this difference did not appear to impact efficacy. However, it should be noted that only a small number of patients remained in the study after 1 year. The results from the current study were used to inform the body surface area (BSA)–based dosing in paediatric patients <40 kg in an ongoing phase 3 study evaluating the safety, efficacy, and pharmacokinetics of ustekinumab in paediatric patients with CD (ClinicalTrials.gov Identifier: NCT04673357). A BSA-based dose adjustment strategy was implemented in paediatric patients with body weight <40 kg to minimise the variability in ustekinumab exposure associated with a mg/kg body weight adjustment dose strategy in this body weight subgroup.

Overall, baseline disease characteristics of the patients evaluated in the LTE period were generally representative of a paediatric population with moderately to severely active CD, with the majority having failed anti-TNF therapy and/or conventional therapy.[16]

As the study was not designed to make any statistical comparisons, only descriptive results were presented. There was a limited number of paediatric patients in the study, and the proportions of patients receiving different doses of ustekinumab were not balanced among those with lower and higher body weight. Approximately 80% of the patients were not receiving any other therapy for CD at the start of the LTE period and the study protocol did not allow the possibility of dose or interval adjustment for those with loss of response and low exposure. Thus, without alternative dosing options, patients were compelled to discontinue study treatment and withdraw from the study to switch to another medication or receive off-label ustekinumab.

In conclusion, the LTE findings suggest that the efficacy and pharmacokinetic profiles through approximately 1 year, and safety and immunogenicity through 4 years of ustekinumab treatment in a paediatric population with CD were generally consistent with those reported for adults.[11,12] Overall, long-term data support the SC dose regimens of 90 mg as maintenance therapy for the treatment of CD for a paediatric population with ≥40 kg body weight. A phase 3 study of ustekinumab (ClinicalTrials.gov Identifier: NCT04673357) is ongoing to further evaluate dose regimens for paediatric patients <40 kg and ≥40 kg. Additional long-term safety evaluation of SC ustekinumab is currently ongoing in the UNITED LTE study (ClinicalTrials.gov Identifier: NCT05092269).

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UniStar Study Group

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CONFLICT OF INTEREST STATEMENT

D. T. received consultation fees, research grants, royalties, or honoraria from Janssen, Pfizer, Hospital for Sick Children, Ferring, AbbVie, Takeda, Biogen, Neopharm Group, Uniliver, Atlantic Health, Shire, Celgene, Eli Lilly and Roche. *J. R. R.* received grant/research support from, served as a consultant for and/or on an advisory board for AbbVie, Janssen, Bristol Myers Squibb, Celgene, Eli Lilly, and Pfizer. *S. A. C.* received grants from and/or served as a consultant for Janssen, Kate Farms, Medtronic, AbbVie, Takeda, Arena, AstraZeneca, and Eli Lilly, and is the chair of a medical advisory committee for Nutrition4IBD, as well as an executive of its parent company, Nutrition4Kids. *A. M. G.* served as a consultant for, served on an advisory board for, received speaker fees from, and/or received research support from AbbVie, Janssen, Bristol Myers Squibb, Celgene, Eli Lilly, Pfizer, Roche, and Nestle. *J. S. H.* served on an advisory board for Janssen, AbbVie, and Eli Lilly, and served as a consultant for Boehringer Ingelheim, Pfizerand Takeda. *J. K.* received grants from Hoffman-La Roche. *O. J. A., R. S., L. K.* and *S. V.* are employees of Janssen Research & Development, LLC and may hold stock in Johnson & Johnson.

DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is 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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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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