P1010

Exposure Optimisation Substudy (EOS) of Ustekinumab in Paediatric Ulcerative Colitis (UC): Q4W Results From the Phase 3 UNIFI Jr Study

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Key Takeaways

- **Ustekinumab q4w dosing led to increased clinical response and remission rates from EOS baseline to Week 16 in the UNIFI Jr substudy**
- **q4w dosing resulted in higher serum ustekinumab concentration in participants who had loss of response after Week 16 and participants who were Week 16 induction non-responders with low steady-state trough ustekinumab concentrations**
  - **The increased ustekinumab concentration was associated with improved mean PUCAI score**
- **No new safety issues were identified**
  - **No deaths occurred and the rate of discontinuation was low**

Background

Ustekinumab therapy induced and maintained response and remission in adult participants with moderate-to-severe ulcerative colitis (UC) in the UNIFI program[1]

UNIFI Jr (NCT04630028) was a Phase 3, multicenter, interventional study in paediatric participants 2 to < 18 years of age with moderately to severely active UC. Participants were randomised to receive ustekinumab every 8 weeks (q8w) and q12w based on baseline weight and induction responder status. Participants who lost response or nonresponders with low ustekinumab steady state serum trough concentration were eligible to enroll into an exposure optimisation substudy (EOS) receiving q4w ustekinumab.

Data from the UNIFI study demonstrated that minimum 8-week steady-state serum trough concentrations of ≥ 1.3 µg/mL ustekinumab were associated with clinical remission[2]
For the UNIFI Jr study, ≥ 1.4 µg/mL was chosen to align with the UNITI Jr study in paediatric participants with Crohn's disease (NCT04673357)

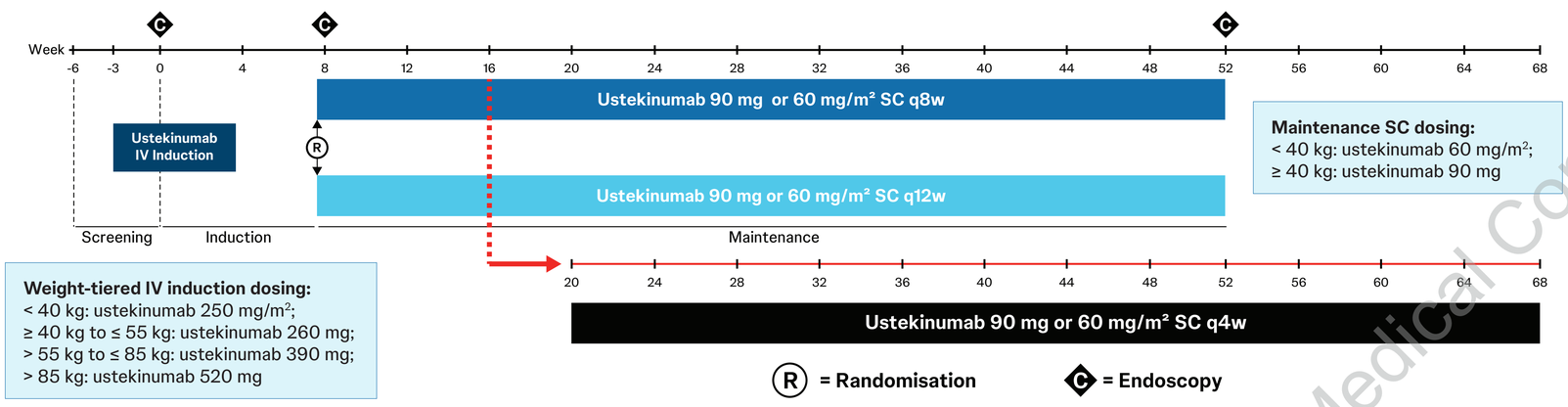
Objective

To examine the efficacy, safety, and pharmacokinetics (PK) of ustekinumab in paediatric participants with moderately to severely active UC in the UNIFI Jr EOS

Methods

UNIFI Jr EOS – Study Design

EOS: UNIFI Jr participants with loss of response after Week 16 and participants who were Week 16 induction non-responders with low steady-state trough ustekinumab concentrations (< 1.4 µg/mL) were eligible for entry in an optional EOS with q4w ustekinumab dosing



Maintenance SC dosing:
< 40 kg: ustekinumab 60 mg/m²;
≥ 40 kg: ustekinumab 90 mg

Weight-tiered IV induction dosing:
< 40 kg: ustekinumab 250 mg/m²;
≥ 40 kg to ≤ 55 kg: ustekinumab 260 mg;
> 55 kg to ≤ 85 kg: ustekinumab 390 mg;
> 85 kg: ustekinumab 520 mg

EOS=exposure optimisation substudy, IV=intravenous, q4w=every 4 weeks, q8w=every 8 weeks, q12w=every 12 weeks, SC=subcutaneous.

Outcomes / Assessments and Analyses

EOS

Primary endpoint
- Clinical remission (PUCAI score < 10) at EOS Week 16

Secondary endpoints
- Clinical response (decrease of ≥ 2 in the partial Mayo response) at EOS Week 16
- Pharmacokinetics during EOS
- Safety

Analysed population
- This analysis was conducted on participants losing response in the UNIFI Jr study and participants who were Week 16 induction non-responders in the UNIFI Jr study with low steady-state trough ustekinumab concentrations (< 1.4 µg/mL)

EOS=exposure optimisation study, PUCAI=Pediatric Ulcerative Colitis Activity Index.

Results

Baseline demographics and disease characteristics of participants in the UNIFI Jr EOS

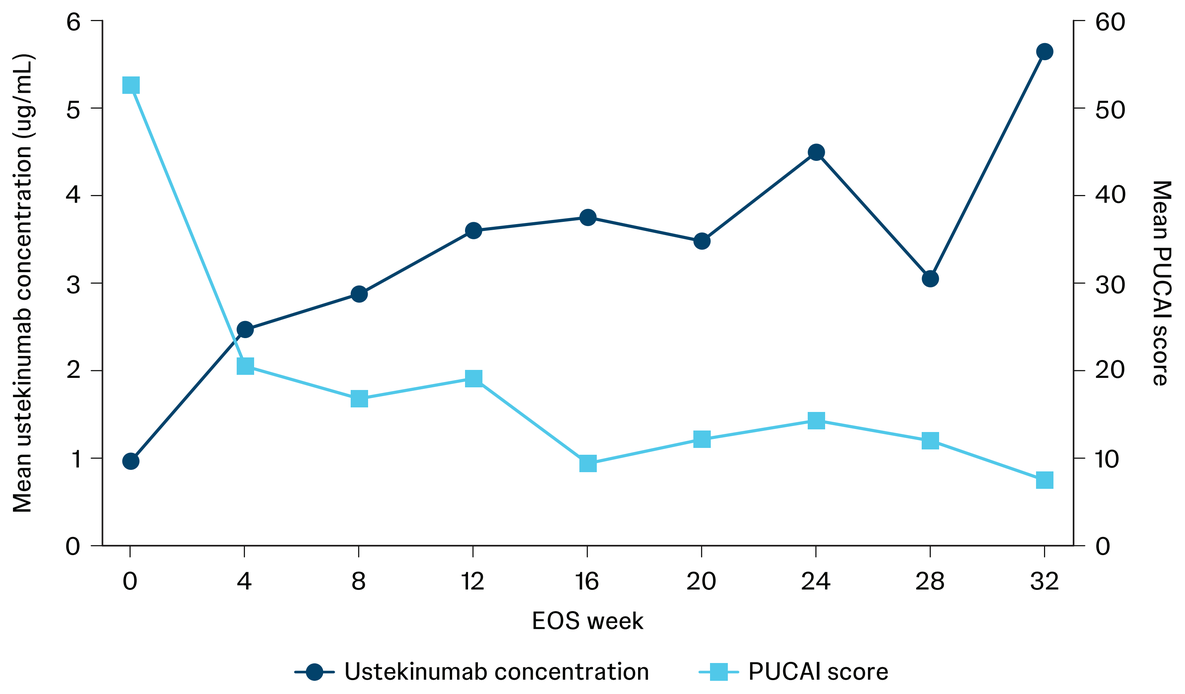
Baseline Characteristics	Total (N = 21)
Demographics	
Age, yrs, median (IQR)	14.0 (9.0, 15.0)
Female, n (%)	7 (33%)
Race, Asian/Black/White, %	14%/0%/81%
BMI, kg/m², mean (SD)	18.3 (3.0)
Disease Characteristics	
Mayo score[a]**,** mean (SD)	8.5 (1.1)
PUCAI score, mean (SD)	47.9 (14.4)
UC disease duration, yrs, mean (SD)	1.9 (1.8)
Abnormal CRP > 3 mg/L, n (%)	12 (57%)
Abnormal faecal calprotectin > 250mg/kg, n (%)	16 (100%)[c]
Prior treatments, n (%)	
Prior biologic failure	12 (57%)
≥1 anti-TNF NOT vedolizumab	9 (43%)
Anti-TNF and vedolizumab	1 (5%)
Prior corticosteroid failure	18 (86%)
Prior immunomodulator failure	9 (43%)

- 21 participants in the primary study were treated in the EOS
- 9 participants from the q8w treatment group and 12 from the q12w group were treated in the EOS
- 15/21 (71%) had moderate disease based on PUCAI score
- 19/19 (100%) had moderate disease based on Mayo score[b]
- EOS population had similar baseline characteristics to the full UNIFI Jr population

[a]Mayo score is based on Central Endoscopy Score [c]2 participants did not have a Mayo score reported at baseline [c]5 participants did not have a faecal calprotectin value reported at baseline.

***BMI**=body mass index, **CRP**=C-reactive protein, **EOS**=exposure optimisation substudy, **IQR**=interquartile range, **PUCAI**=Pediatric Ulcerative Colitis Activity Index, **SD**=standard deviation, **TNF**=tumor necrosis factor, **UC**=ulcerative colitis.*

Elevated serum concentration of ustekinumab may be associated with improved PUCAI scores

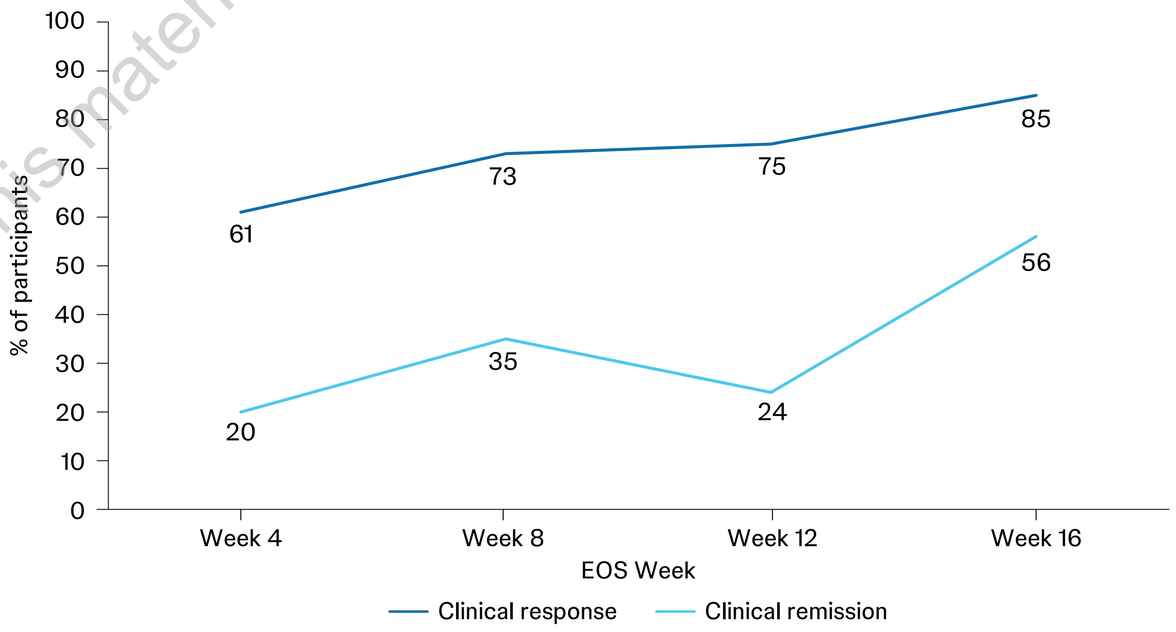


- The median/mean [range] PUCAI score at Week 16 was 2.5/9.4 [0; 50] (change-from-baseline: -47.5/-43.4 [-65; -10])
- Week 8 steady-state ustekinumab concentration prior to EOS visit was (median/mean [IQR]): 0.617/0.671 [0.38; 1.03] µg/mL

[c]5 participants discontinued treatment.

***EOS**=exposure optimisation study, **IQR**=interquartile range, **PUCAI**=Pediatric Ulcerative Colitis Activity Index.*

Clinical outcomes improved over time during the EOS



- 16/21 (76%) completed ≥ 16 weeks of treatment in the EOS
- At Week 16 of the EOS, 9/16 (56%) achieved clinical remission based on PUCAI score; 11/13 (85%) achieved clinical response based on partial Mayo score[a]

[a]3 participants did not have a partial Mayo score at Week 16.

***EOS**=exposure optimisation study.*

Serum ustekinumab concentrations were similar between paediatric and adult participants

Following q4w dosing, at EOS Week 16
- Steady-state ustekinumab concentration increased from (median/mean) 0.38/0.97 µg/mL (IQR: 0.00; 1.86) at EOS Week 0 before administration of the first q4w dose to 2.28/3.75 µg/mL (IQR: 1.97; 5.29) at EOS Week 16

Historically, in the UNIFI study, among adults dosed q8w at Week 16
- Steady-state ustekinumab concentration was (median/mean) 2.69/3.28 µg/mL (IQR: 1.53; 4.48)

*IQR=interquartile range, **q4w**=every 4 weeks, **q8w**=every 8 weeks.*

The safety profile was consistent with the primary UNIFI Jr study

Safety through the end of EOS	EOS (N=21)
Average weeks of follow-up	23.5
Any AE	17 (81%)
GI-related AE	6 (29%)
Any SAE	2 (10%)
Most common AEs (≥ 5%)	
Upper respiratory tract infection	6 (29%)
Colitis ulcerative	4 (19%)
Anaemia	4 (19%)
Iron deficiency anaemia	3 (14%)
Nasopharyngitis	2 (10%)
Respiratory tract infection	2 (10%)

- Safety was generally consistent with the primary study
- No new safety signals were identified in the EOS
- No deaths occurred during the EOS
- 1 (4.8%) substudy participant discontinued study treatment due to an AE of colitis ulcerative during the EOS

*AE=adverse event, **EOS**=exposure optimisation study, **GI**=gastrointestinal, **SAE**=serious adverse event.*

PRESENTED AT: 21st Congress of ECCO, February 18–21, 2026, Stockholm, Sweden. **REFERENCES: 1.** Sands BE, et al. *N Engl J Med.* 2019;381:1201–1214. **2.** Adedokun OJ, et al. *Clin Gastroenterol Hepatol.* 2020;18:2244–2255. **ACKNOWLEDGMENTS:** Medical writing support was provided by Amy C. Porter, PhD, of Certara under the direction of the authors in accordance with Good Publication Practice guidelines (*Ann Intern Med.* 2022;175:1298–1304) and funded by Johnson & Johnson. This presentation was sponsored by Johnson & Johnson. **DISCLOSURES: EDG:** served on an advisory board of Johnson & Johnson. **RKR:** received consultation fees, research grant, royalties, or honorarium from Johnson & Johnson, Pfizer, Ferring, Celltrion, Lilly, AlfaSigma & Pharmacosmos. **DT:** received consultation fee, research grant, royalties, or honorarium from Johnson & Johnson, Pfizer, Shaare Zedek Medical Center, Hospital for Sick Children, Ferring, AbbVie, Takeda, Prometheus Biosciences, Lilly, Sorriso Pharma, Boehringer Ingelheim, Galapagos, BMS, AlfaSigma, and Merck. **AMG:** received consultation fee, research grant, royalties or honorarium from AbbVie, Alfasigma, Johnson & Johnson, Lilly, Merck, Pfizer, Shaare Zedek Medical Centre, SickKids Hospital, Takeda. **JSH:** serves/served on advisory board for Johnson & Johnson, Lilly; was/is a consultant for Takeda, Roche, and Boehringer Ingelheim. **SAC:** served as a consultant for Johnson & Johnson. **JRR:** served/serves as an advisor and consultant for AbbVie; serves/served as an advisor, consultant, and medical monitor for Johnson & Johnson. **JK:** received a grant from Nestle for the study research conducted. **BK:** received a grant from Johnson & Johnson for the study research conducted. **MM:** received consultation fees, royalties from Sandoz and Ferring. **RS, EVL, LSC, OJA, JS, YW,** and **PJU:** Employees of Johnson & Johnson; may own stock/stock options in Johnson & Johnson.