Exposure Optimization Substudy (EOS) of Ustekinumab in Pediatric 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 pediatric participants 2 to < 18 years of age with moderately to severely active UC. Participants were randomized 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 optimization substudy (EOS) receiving q4w ustekinumab.

Data from the UNIFI study demonstrated that minimum 8-week steady-state serum trough concentrations of ustekinumab ≥ 1.3 µg/mL 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 pediatric participants with Crohn's disease (NCT04673357)

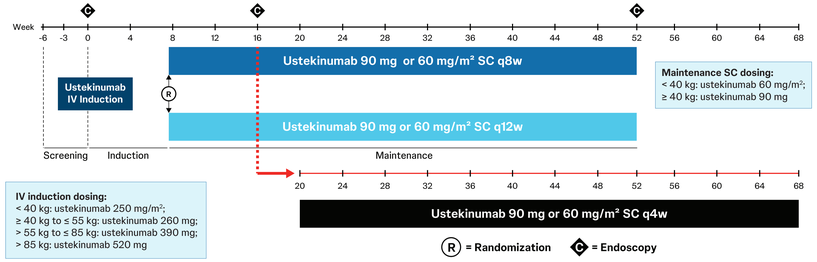
Objective

To examine the efficacy, safety, and pharmacokinetics (PK) of ustekinumab in pediatric 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

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 optimization 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
Analyzed population	• 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 optimization substudy, **PUCAI**=Pediatric Ulcerative Colitis Activity Index.*

Results

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

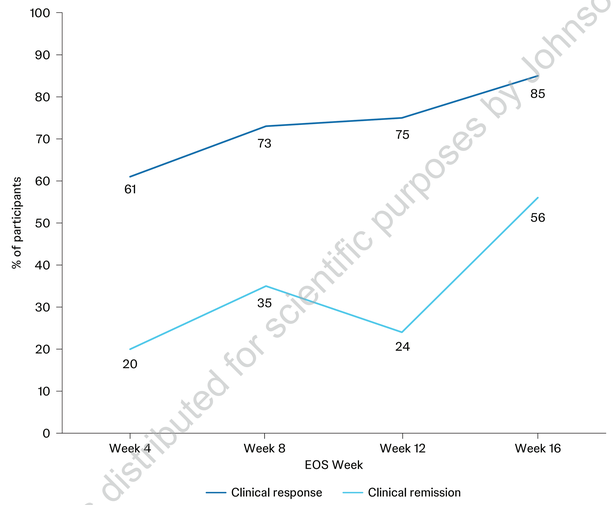
Baseline Characteristics	Total (N = 21)
Demographics	
Age, yrs, median (IQR)	14.0 (9.0, 15.0)
Female, n (%)	7 (33%)
Race, Asian/Black/White, %	14%/0%/81%
BMI, kg/m², mean (SD)	18.3 (3.0)
Disease Characteristics	
Mayo score[a,b]**,** mean (SD)	8.5 (1.1)
PUCAI score, mean (SD)	47.9 (14.4)
UC disease duration, yrs, mean (SD)	1.9 (1.8)
Abnormal CRP > 3 mg/L, n (%)	12 (57%)
Abnormal fecal calprotectin > 250 mg/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 fecal calprotectin value reported at baseline.

***BMI**=body mass index, **CRP**=C-reactive protein, **EOS**=exposure optimization substudy, **IQR**=interquartile range, **PUCAI**=Pediatric Ulcerative Colitis Activity Index, **q8w**=every 8 weeks, **q12w**=every 12 weeks, **SD**=standard deviation, **TNF**=tumor necrosis factor, **UC**=ulcerative colitis.*

Clinical outcomes improved over time during the EOS

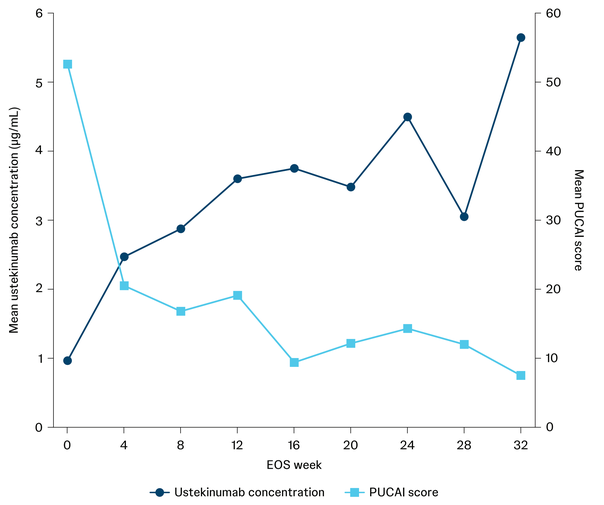


- 16/21 (76%) completed ≥ 16 weeks of treatment in the EOS
- At Week 16 of the EOS, 9/16 (56%) achieved clinical remission based on PUCAI score; 11/13 (85%) achieved clinical response based on partial Mayo score[a]

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

***EOS**=exposure optimization substudy, **PUCAI**=Pediatric Ulcerative Colitis Activity Index.*

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

***EOS**=exposure optimization substudy, **IQR**=interquartile range, **PUCAI**=Pediatric Ulcerative Colitis Activity Index.*

Serum ustekinumab concentrations were similar between pediatric 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)

***EOS**=exposure optimization substudy, **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%)
Anemia	4 (19%)
Iron deficiency anemia	3 (14%)
Nasopharyngitis	2 (10%)
Respiratory tract infection	2 (10%)

***AE**=adverse event, **EOS**=exposure optimization substudy, **GI**=gastrointestinal, **SAE**=serious adverse event.*

- 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

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