Dose Escalation in Participants With Primary/ Secondary Loss of Response to Conventional Dosing of Ustekinumab in Paediatric Crohn's Disease (UNITI Jr Study)

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Key Takeaways

- **Majority of the paediatric participants who had shortened dose interval to q4w were in clinical response and half achieved clinical remission 16 weeks after switching to ustekinumab q4w dosing plus improvements in inflammatory markers after 16 weeks**
- **Switching to q4w dosing in paediatric participants resulted in higher serum concentrations of ustekinumab and led to ustekinumab exposures that fell within the safe and effective exposure range observed in adult CD ustekinumab studies**
- **No new safety issues were identified. The safety profile of ustekinumab administered to participants q4w was consistent with the safety profile in the main UNITI Jr study plus improvements in inflammatory markers after 16 weeks.**

Background

Ustekinumab therapy induced and maintained response and remission in adult patients with moderate-to-severe Crohn's disease (CD) in the IM-UNITI program[1,2]

Data from IM-UNITI demonstrated that minimum steady-state serum trough concentrations of ≥1.4 µg/mL ustekinumab were associated with clinical remission[3]
The shortening of ustekinumab dosing intervals is regularly utilized in clinical practice and has been shown to be effective in real-world paediatric studies[4]

UNITI Jr was a phase 3 multicenter study in paediatric patients (≥2 to <18 years) with moderately to severely active CD, consisting of one open-label intravenous (IV) dose of ustekinumab followed by randomized double-blind subcutaneous (SC) maintenance dosing every 8 weeks (q8w) or every 12 weeks (q12w) starting at week 8[5]
An optional exposure optimization substudy (EOS) was offered to nonresponders and induction responders and delayed responders who lost response during maintenance and who had low serum ustekinumab concentration (<1.4).
EOS participants received open-label q4w dosing for a minimum of 16 weeks

Objective

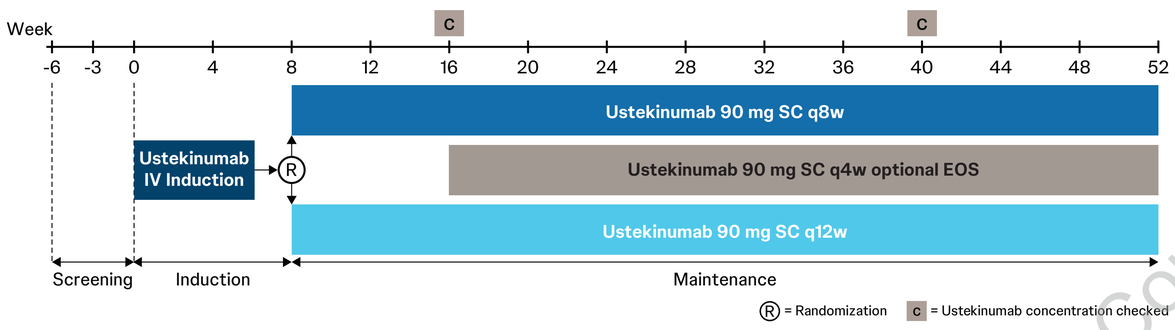
To examine efficacy, safety, and pharmacokinetics of ustekinumab dose interval shortening in paediatric participants with moderate-to-severe CD in the UNITI Jr (NCT04673357) Exposure Optimization Substudy (EOS)

Methods

UNITI Jr Exposure Optimization Substudy – Study Design

Key inclusion criteria for the UNITI Jr study:

- ✓ Paediatric participants ≥2 to <18 years old with a Paediatric Crohn's Disease Activity Index (PCDAI) score of >30
- ✓ Inadequate response/intolerance to biologic therapies (TNFα antagonist or vedolizumab), IV or oral corticosteroids (including corticosteroid dependence), or immunosuppressants (6-MP/AZA/MTX)
- ✓ Ileocolonoscopic ulceration or increased C-reactive protein (CRP ≥3.0 mg/L) or calprotectin (≥250 µg/g)



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 eligibility criteria: Participants who were induction non-responders and had low steady-state trough ustekinumab concentrations (<1.4 µg/mL) at Week (WK) 16 or participants losing response after WK16 and who had corresponding low steady-state trough ustekinumab concentrations at WK16 or WK40.[a]

[a]Participants could enter the EOS at various times. ***AZA****=azathioprine,* ***EOS****= exposure optimization substudy,* ***IV****=intravenous,* ***6-MP****=6-mercaptopurine,* ***MTX****=methotrexate,* ***q4w****=every 4 weeks,* ***q8w****=every 8 weeks,* ***q12w****=every 12 weeks,* ***SC****=subcutaneous,* ***TNFα****=tumor necrosis factor alpha.*

Outcomes / Assessments and Analyses for the Exposure Optimization Substudy

EOS (Weeks 1-16)

Major endpoints

- Clinical remission at EOS Week 16
- Clinical response at EOS Week 16
- Pharmacokinetics during EOS
- Safety (Occurrence and severity of adverse events, serious adverse events and laboratory values)

Analyzed population

- These analyses were conducted in all participants who entered the EOS and had data at/through EOS Week 16

EOS*=exposure optimization study.*

Results

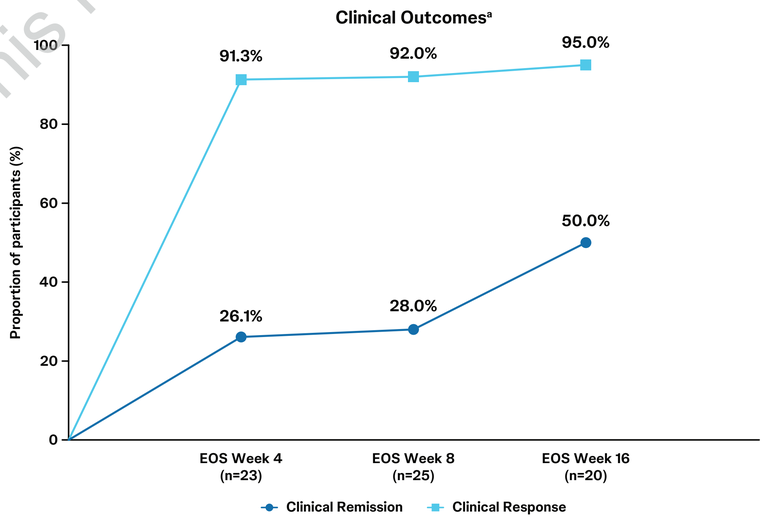
Baseline demographics and disease characteristics of EOS participants

Baseline Characteristics		Total (N = 26)
Demographics		
	Age, yrs, median (IQR)	14.0 (12.0, 16.0)
	Female, n (%)	46.2%
	Race, Asian/Black/White, n (%)	7.7/3.8/88.5%
	Weight, kg, median (IQR)	48.8 (39.6, 59.8)
	BMI-Z score, median (IQR)	-0.16 (-0.82, 0.44)
Disease Characteristics, mean (SD)		
	PCDAI score	42.6 (8.0)
	sPCDAI score	56.0 (12.2)
	sPCDAI score at EOS Week 0	49.2 (14.1)
	CRP, mg/L	21.5 (27.0)
	CRP at EOS Week 0, mg/L	20.3 (27.2)
	CD disease duration, yrs	3.0 (2.0)
	Fecal calprotectin, mg/kg	2741.3 (1853.6)
Prior treatments, n (%)		
	Prior biologic failure	21 (80.8%)
	≥1 anti-TNF NOT to vedolizumab	20 (76.9%)
	Anti-TNF and vedolizumab	1 (3.8%)
	Prior corticosteroid failure	13 (50.0%)
	Prior immunomodulator failure	16 (61.5%)

Data shown are mean (SD) unless otherwise noted. ***BMI****=body mass index,* ***CD****=Crohn's disease,* ***CRP****=c-reactive protein,* ***EOS****=exposure optimization study,* ***IQR****=interquartile range,* ***PCDAI****=Paediatric Crohn's Disease Activity Index,* ***sPCDAI****=short Paediatric Crohn's Disease Activity Index,* ***TNF****=tumor necrosis factor.*

- Of 97 randomized participants in main study, 26 (26.8%) enrolled in EOS, 15 participants from the q8w cohort and 11 from the q12w cohort
- 3 participants were randomized induction non-responders with low ustekinumab levels by Week I-8 and 23 had a confirmed loss of response
- 14/26 [53.8%] had PCDAI >40 at main study baseline
- A larger proportion of participants in the EOS had a history of biologic failure, with 21/26 [80.8%] compared with 57/101 (56.4%) in the main study
- At the substudy baseline (EOS Week 0), upon initiation of the q4w dose regimen, the short PCDAI (sPCDAI) scores and the CRP concentration were consistent with loss of response and moderately to severely active disease

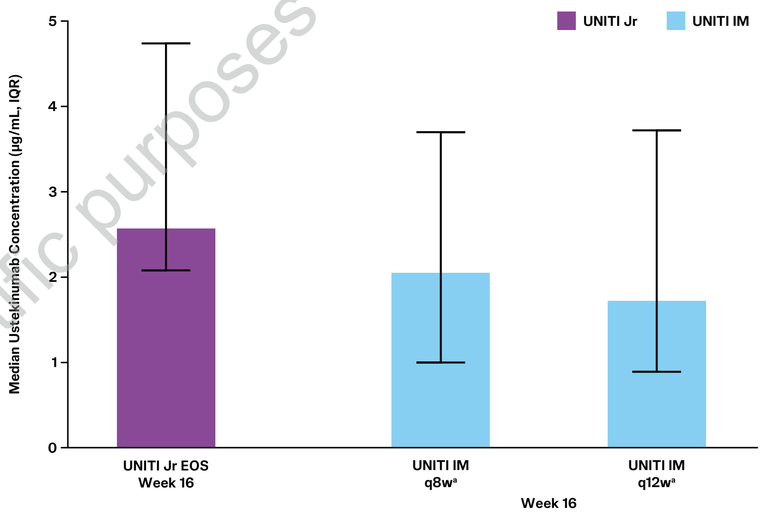
Clinical outcomes improved over time during the EOS



[a]Observed data was used, [b]Clinical remission is defined as PCDAI score ≤10 points, [c]Clinical response is defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30. ***EOS****=exposure optimization study,* ***PCDAI****=Paediatric Crohn's Disease Activity Index.*

- 21 (80.8%) completed ≥16-weeks of EOS treatment
- EOS Week 16, 10/20 achieved clinical remission; 19/20 achieved clinical response

Serum ustekinumab concentrations at EOS Week 16 were similar to the concentrations observed in the adult CD study



[a]Data from Feagan BJ, et al. N Engl J Med. 2016;375(20):1946–1960. ***EOS****=exposure optimization substudy,* ***IQR****=interquartile range,* ***q4w****=every 4 weeks,* ***q8w****=every 8 weeks,* ***q12w****=every 12 weeks.*

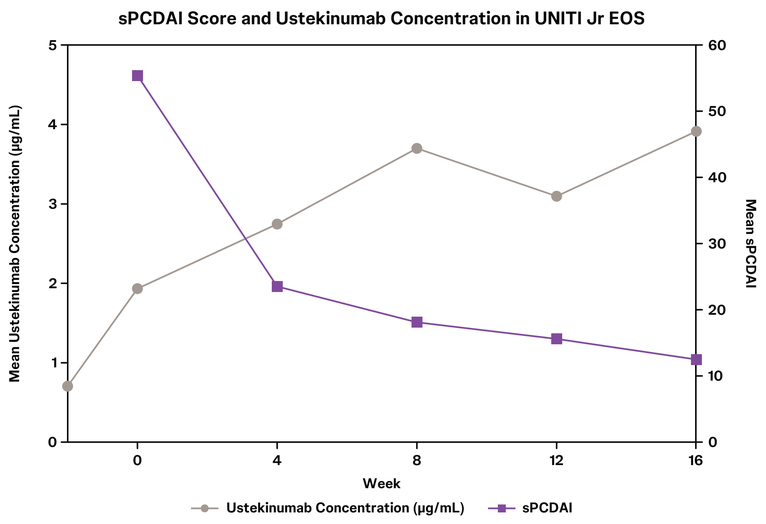
Steady-state ustekinumab concentration at EOS Week 16

- q4w dosing: median 2.57 µg/mL ([Interquartile range]: 2.08; 4.74)

Historically, in the UNITI IM study, steady-state ustekinumab concentrations in adults at Week 16[a]

- q8w dosing: median 2.05 µg/mL (IQR: 1.00, 3.70)
- q12w dosing: median 1.72 µg/mL (IQR: 0.89, 3.72)

Increased serum concentration of ustekinumab were associated with improved sPCDAI scores



EOS*=exposure optimization study,* ***sPCDAI****=short Paediatric Crohn's Disease Activity Index.*

- The mean standard deviation (SD) ustekinumab concentration prior to the start of the substudy was 0.7 (0.5) µg/mL
- As mean ustekinumab exposure increased with the q4w dose regimen, an improvement in efficacy was observed based on mean sPCDAI scores
- The median/mean [range] sPCDAI score at EOS Week 16 was 10.0/12.5 [0; 45] (change-from-baseline: -40.0/-37.5 [−70; 5])

The safety profile was within expectations

Safety through the end of EOS	EOS (N=26)
Mean weeks of follow-up	20.4
Any AE	19 (73.1%)
Any SAE	3 (11.5%)
Infections	12 (46.2%)
Serious infections[a]	3 (11.5%)
Opportunistic infections[b]	1 (3.8%)
Discontinuations due to AE	2 (7.7%)
Most common AEs (≥5%)[c]	
Crohn's disease	4 (15.4%)
Upper respiratory tract infection	3 (11.5%)
Fatigue	3 (11.5%)
Nausea	2 (7.7%)
Rhinitis	2 (7.7%)
Pyrexia	2 (7.7%)
Rhinitis allergic	2 (7.7%)
Iron deficiency anaemia	2 (7.7%)

[a]1 participant reported events of terminal ileitis with abscess formation; 1 participant reported pyrexia post-ileocolonoscopy; 1 participant reported gastroenteritis aeromonas (reported term of "worsening gastroenteritis with aeromonas species"); [b]cytomegalovirus colitis; [c]2 participants reported AEs reasonably related to the study drug. ***AE****=adverse event,* ***EOS****=exposure optimization study,* ***SAE****=serious adverse event.*

- Safety was generally consistent with the main study
- No new safety signals were identified
- The most frequently reported adverse events were gastrointestinal-related, reported in 10 (38.5%) of participants
- No malignancies, tuberculosis and deaths occurred during the study

Laboratory values at EOS Week 16 and changes from EOS baseline compared with Week 52 of UNITI Jr main study, mean (range)

	EOS Week 16 [CFB]	Week 52 [CFB][a]
C-reactive protein, mg/L	2.75 (0.1 — 7.8) [−9.22 (−64.5 — 0)]	6.07 (0.1 — 57.2) [−10.74 (−102.5 — 11.6)]
Hematocrit	0.380 (0.30 — 0.43) [0.011 (−0.02 — 0.05)]	0.392 (0.32 — 0.49) [0.028 (−0.06 — 0.12)]
Platelets, x10⁹/L	353.1 (238 — 655) [−48.9 (−136 — 29)]	330.8 (154 — 542) [−77.3 (−389 — 211)]
Albumin, g/L	43.5 (36 — 48) [1.9 (−4 — 8)]	45.1 (34 — 55) [3.4 (−4 — 16)]
ESR, mm/hr	28.3 (3 — 83) [−4.4 (−28 — 38)]	21.9 (2 — 73) [−16.1 (−75 — 30)]
Faecal lactoferrin, µg/g	423.9 (1.8 — 1000.0) [−115.4 (−998.2 — 794.9)]	182.63 (0.41 — 1000.0) [−59.06 (−996.38 — 420.61)]

[a]Change from maintenance period baseline at Week 8. ***CFB****=change from baseline,* ***EOS****=exposure optimization study,* ***ESR****=erythrocyte sedimentation rate.*

- Laboratory parameters of inflammation and faecal lactoferrin improved from EOS baseline to Week 16 and were similar to Week 52 of the main study

Limitations of the EOS

- Participants entered the EOS at different timepoints and were enrolled for varying durations
- There was no endoscopic evaluation at entry and exit of the EOS

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