Safety and Efficacy of Ustekinumab in Indian Patients with Moderate to Severe Crohn's Disease: A Multicentre, Interventional, Phase IV study

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Summary

- **No new safety signals were identified during the study. Most TEAEs were mild in severity and did not necessitate discontinuation of study intervention. No treatment-emergent opportunistic infections, active tuberculosis, or malignancies were reported.**
- **CDAI analyses demonstrated a clinically meaningful effect of ustekinumab in inducing and maintaining clinical response and remission, with remission rates increasing from Week 16 to Week 24 during subcutaneous maintenance therapy. Overall, Ustekinumab was well-tolerated and clinically effective in Indian patients with moderate to severe CD.**

Conclusion

- **Ustekinumab demonstrated a favourable safety profile and clinical efficacy in patients with moderate to severe CD, supporting its use as an effective therapeutic option for Indian patients.**

Background

- Ustekinumab (STELARA®), a human IgG1κ monoclonal antibody that targets the p40 subunit of IL-12/ IL-23 cytokines[1] is approved globally in multiple countries including United States, EU and India for the treatment of moderate to severe Crohn's disease (CD).[2,3]
- Clinical studies demonstrated the efficacy and favourable safety profile of ustekinumab, with high response rates and sustained remission during maintenance therapy.[4–7] Despite extensive global evidence, real-world data on the safety and effectiveness of ustekinumab in the Indian patient population remains limited.
- This health authority mandated Phase IV study aimed to evaluate the safety and clinical efficacy of UST in adult Indian patients with moderate to severe CD.

Objective

- **Primary Objective:** **To evaluate the safety of ustekinumab in patients with moderate to severe CD over 38 weeks.**
- **Secondary Objective:** **To evaluate the efficacy of ustekinumab in moderate to severe CD patients, as assessed by CD activity index (CDAI).**
- **Exploratory Objective:** **To evaluate the effect of ustekinumab on biomarkers of inflammation (C-Reactive protein [CRP] and fecal calprotectin [FCP]).**

Methods

Study design: Phase 4, open-label, multicentre study **(Figure 1)**

Key eligibility criteria

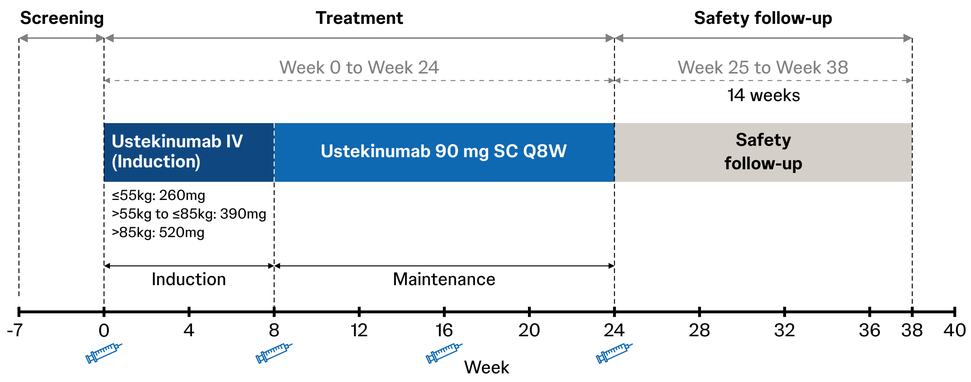
Inclusion criteria

- ✓ Male or female patients aged ≥18 years with a diagnosis of moderate to severe Crohn's disease for ≥3 months, with a baseline Crohn's Disease Activity Index (CDAI) score of 220–450.
- ✓ Failure, intolerance, or dependence on corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate, including but not limited to 6-thioguanine, cyclosporine, mycophenolate mofetil, tacrolimus, or sirolimus), or biologic therapies (anti-tumor necrosis factor agents or vedolizumab).
- ✓ No prior tuberculosis (TB) history, symptoms, or recent exposure with active TB. Negative QuantiFERON-TB Gold and tuberculin skin tests within 6 weeks before first intervention, or newly positive results with active TB and latent TB treatment initiated. Chest radiograph showing no evidence of active or inactive TB.

Exclusion criteria

- ✗ Prior exposure to ustekinumab or known hypersensitivity to ustekinumab or other interleukin (IL)-12 or IL-23 antagonists, or its excipients.
- ✗ Crohn's disease complications that required surgery, precluded accurate CDAI assessment, or could confound evaluation of treatment response.
- ✗ Clinically significant active predefined infections and serious infections.
- ✗ Known malignancy, history of malignancy, or history of lymphoproliferative disease, except for adequately treated non-melanoma skin cancer or carcinoma in situ of the cervix.

Figure 1: Study design



***IV**=Intravenous, **SC**=Subcutaneous, **Q8W**=Every 8 weeks.*

- **Sites:** 10 centres across India
- **Follow-up:** End-of-study visit at Week 38

Endpoints

Primary endpoint

- Safety (number and percentage of adverse events [AEs] or serious AEs).

Secondary endpoints

- Clinical remission (defined by CDAI score <150) at Weeks 8, 16, and 24.
- Clinical response (defined by decrease of 100 or more on the CDAI score or a total CDAI score <150) at Weeks 8, 16, and 24.

Exploratory endpoints

- Change in CRP levels at Week 8 and Week 24 from baseline.
- Change in FCP levels at Week 8 and Week 24 from baseline.

Statistical analyses

- The planned sample size was based on safety considerations and feasibility for a Phase IV study.
- All enrolled patients who received at least one dose of Ustekinumab were included in the safety analysis set.
- The efficacy analysis set included patients with available CDAI assessments at baseline and at least one at post-treatment visit.
- Missing data were handled using observed case analysis. Data were summarized as counts and percentages with corresponding 95% confidence intervals (CIs) for categorical variables, and as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables.

Results

Patient disposition

- A total of 96 patients were screened for the study (All Patients Set). Of these, 80 patients (83.3%) were enrolled and received study treatment (Safety Analysis Set), while 16 patients (16.7%) were screen failures based on inclusion and exclusion criteria. Of the enrolled patients, 74 (92.5%) completed study participation, and 6 (7.5%) discontinued the study.

Table 1: Baseline Demographic and Disease Characteristics (Safety Analysis Set)

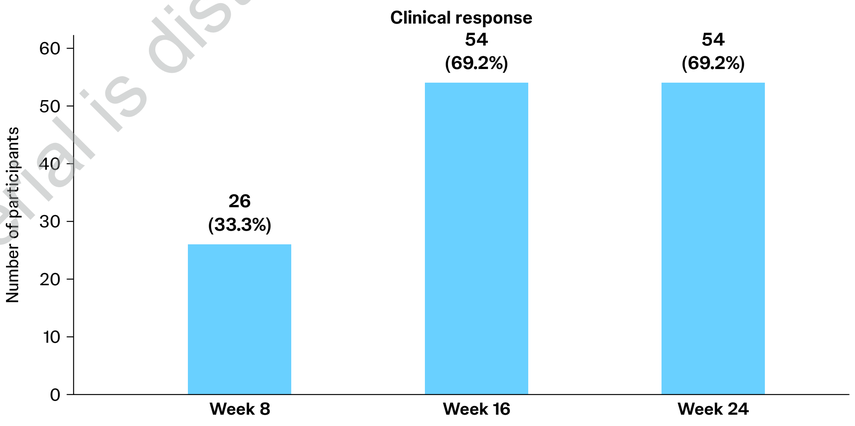
Baseline Characteristics	Total (N=80)
Demographics	
Age, yrs, mean (SD)	35.3 (14.4)
BMI, kg/m^2, mean (SD)	19.27 (3.6)
Gender, n (%)	
Male	52 (65)
Female	28 (35)
Disease Characteristics	
Disease duration, yrs, Median (IQR)	2.6 (1.3–7.4)
CDAI score, mean (SD)	296.2 (52.5)
Patients with CDAI >300, n (%)	39 (48.8)
Prior CD therapy exposure, n (%)	66 (82.5)
Biologic naïve, n (%)	62 (77.5)
Conventional therapy failure/intolerance (Yes; n [%])	76 (95)
Biologics failure/intolerance (Yes; n [%])	18 (22.5)
CRP, mg/L	12.8 (30.5)
FCP, mg/kg	717.5 (1216)

***BMI**=Body mass index, **CD**=Crohn's disease, **CDAI**=Crohn's disease activity index, **CRP**=C-reactive protein, **FCP**= Fecal calprotectin, **n**=number of patients, **%**=percentage, **SD**=Standard Deviation, **IQR**=Interquartile range.*

Clinical Efficacy

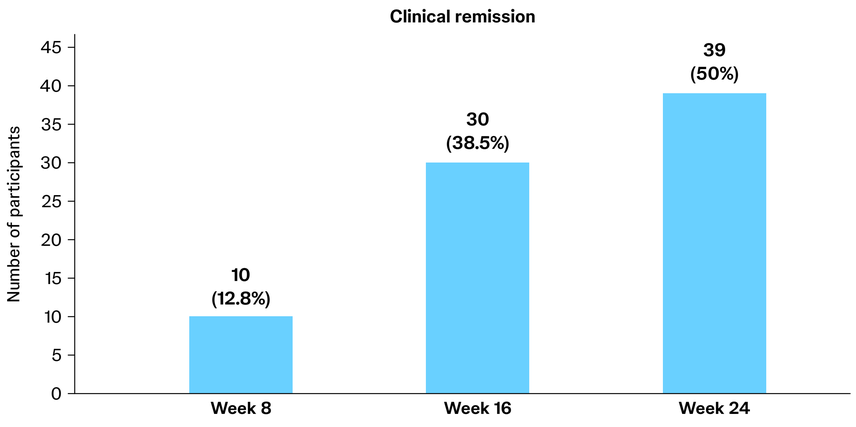
- **Clinical Response:** The clinical response rate increased from 33.3% at Week 8 to 69.2% at Week 16 and was maintained at Week 24, demonstrating a sustained treatment effect.

Figure 2: Number of patients achieving clinical response at Weeks 8, 16, and 24 following ustekinumab treatment



- **Clinical Remission:** Remission rates increased progressively from 12.8% at Week 8 to 38.5% at Week 16 and 50% at Week 24, indicating continued improvement over time.

Figure 3: Number of patients achieving clinical remission at Weeks 8, 16, and 24 following ustekinumab treatment



Inflammatory Biomarkers

- After a single dose of ustekinumab induction therapy, mean CRP and FCP levels decreased from baseline to Week 8 and this effect was maintained at Week 24.

Figure 4: Mean levels of (a) CRP and (b) FCP at baseline, Week 8 and Week 24

(a) CRP

(b) FCP

***CRP**=C-reactive protein, **FCP**=Fecal Calprotectin.*

Safety Outcomes

Table 2: Summary of Adverse Events (Safety Analysis Set)

AEs	Patients, n (%)
Total patients	80
Patients with ≥1 AE	29 (36.3)
Related TEAEs	2 (2.5)
TEAEs leading to death	1 (1.3)
Serious TEAEs	2 (2.5)
Related serious TEAEs	2 (2.5)
TEAEs leading to discontinuation of study intervention	1 (1.3)
TE infections (Gastroenteritis [n=2], Gastric infection [n=1], and Liver abscess [n=1])	4 (5.0)
Opportunistic infections	0 (0)
Active tuberculosis	0 (0)
TE infusion or injection-site reactions	1 (1.3)
Common AEs (≥5%)	
Anaemia	16 (20.0)
Pyrexia	6 (7.5)

***AE**=Adverse events, **n**=number of patients, **TE**=Treatment-emergent, **%**=percentage.*

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