A Multicenter, Double-blind, Placebo-controlled Phase 3 Study of Ustekinumab, a Human IL-12/23p40 Monoclonal Antibody, in Moderate-severe Crohn’s Disease Refractory to Anti-TNFα: UNITI-1

WJ Sandborn¹, C Gasink², M Blank³, Y Lang², J Johanss², LL Gao², BE Sands⁴, S Hanauer⁵, B Feagan⁶, S Targan⁷, S Ghosh⁸, W de Villiers⁹, JF Colombel⁴, SD Lee¹⁰, P Desreumaux¹¹, EV Loftus, Jr.¹², S Vermeire¹³, P Rutgeerts¹⁴

¹UCSD, La Jolla, CA, USA, ²Janssen Research & Development, Spring House, PA, USA, ³Janssen Pharmaceuticals, Inc, Horsham, PA, USA, ⁴Mt. Sinai Medical Center, NY, NY, USA, ⁵Northwestern University, Chicago, IL, USA, ⁶Robarts Research Institute, London, Ontario, Canada, ⁷Cedars-Sinai Medical Center, Los Angeles, CA, USA, ⁸University of Calgary, Calgary, Alberta, Canada,
⁹U of Cape Town, South Africa, ¹⁰U of Washington, Seattle, WA,USA, ¹¹CHRU de Lille, Hôpital Claude Huriez, Lille, France, ¹²Mayo Clinic, Rochester, MN, USA, ¹³University Hospitals, Leuven, Belgium, ¹⁴University Hospital Gasthuisberg, Leuven, Belgium
Ustekinumab Background

- IL-12 & IL-23 are key cytokines in the pathogenic immune cascade of Crohn’s disease
- Ustekinumab is a fully human IgG1k monoclonal antibody binding the p40 subunit of Interleukins-12 & 23
- Inhibits IL-12- and IL-23-mediated signaling, cellular activation, and downstream cytokine production
- Approved for moderate to severe psoriasis and psoriatic arthritis
- Induction efficacy in primarily anti-TNF naïve prior conventional therapy failures recently demonstrated in UNITI-2 Study


UNITI-1

Overall UNITI Phase 3 Crohn’s Program

**Two Induction Studies**

**UNITI-1: ±TNF Failure Population**
- Placebo IV (N=225)*
- Ustekinumab 130 mg IV (N=225)*
- Ustekinumab ~6 mg/kg IV (N=225)*

**UNITI-2: Failed Convent. Therapy**
- Ustekinumab 130 mg IV (N=200)*
- Ustekinumab ~6 mg/kg† IV (N=200)*
- Placebo IV (N=200)*

**One Maintenance Study**

**IM-UNITI**
Randomized Withdrawal Maintenance Study

- Responders
  - 90 mg SC q8 wks
  - 90 mg SC q12 wks
  - Placebo SC

44 Week maintenance study: Followed by (up to) 4 yr LTE

*Subjects randomized to placebo and subjects who are non-responders to ustekinumab are eligible for non-randomized maintenance dosing after completion of the induction study.

Study Population and Objective

- **The UNITI-1 Study Enrolled:**
  - Patients with moderately to severely active Crohn’s disease (CDAI score 220-450) of ≥ 3 months duration who previously received and failed one or more approved anti-TNF therapy regimen because of:
    - Not initially responding (i.e., primary non-response)
    - Losing Response after initial response (i.e., secondary non-response) OR
    - Were intolerant to the medication
  - Criteria identical to previous Phase 2b CERTIFI Study

- **Objective of this Phase 3 Study:**
  - To evaluate efficacy and safety of IV ustekinumab induction in patients who have failed one or more anti-TNF
UNITI-1 Study Design

- **Ustekinumab 130 mg IV**
- **Weight-based ustekinumab ~6 mg/kg IV**
  - 260 mg (≤ 55 kg)
  - 390 mg (56-85 kg)
  - 520 mg (> 85 kg)

- Placebo IV

- 0 3 6 8
  - Primary Endpoint
  - Enter IM-UNITI maintenance study

- **Randomization**
- **Study agent administration**

Screening

Key Endpoints

• **Primary Endpoint:**
  Clinical Response at Week 6, defined as a reduction from baseline in the CDAI score of $\geq 100$ points or CDAI
  - Subjects with at least 100 point drop or CDAI < 150

• **Major Secondary Endpoints:**
  - Clinical Remission (CDAI <150) at Week 8
  - Clinical Response at Week 8
  - 70-point CDAI response at Week 6
  - 70-point CDAI response at Week 3
### Baseline Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ustekinumab 130 mg</th>
<th>~6 mg/kg</th>
<th>Combined</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects randomized</strong></td>
<td>247</td>
<td>245</td>
<td>249</td>
<td>494</td>
<td>741</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>36.0</td>
<td>37.0</td>
<td>36.0</td>
<td>36.0</td>
<td>36.0</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>47.8</td>
<td>40.0</td>
<td>40.6</td>
<td>40.3</td>
<td>42.8</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>69.1</td>
<td>65.9</td>
<td>66.0</td>
<td>66.0</td>
<td>67.0</td>
</tr>
<tr>
<td><strong>CDAI score</strong></td>
<td>313.0</td>
<td>318.0</td>
<td>319.0</td>
<td>319.0</td>
<td>317.0</td>
</tr>
<tr>
<td><strong>CD duration (years)</strong></td>
<td>9.7</td>
<td>9.9</td>
<td>11.0</td>
<td>10.3</td>
<td>10.1</td>
</tr>
<tr>
<td><strong>CRP (mg/L)</strong></td>
<td>8.5</td>
<td>10.4</td>
<td>9.9</td>
<td>10.2</td>
<td>9.9</td>
</tr>
<tr>
<td><strong>Abnormal CRP (%)</strong></td>
<td>77.7</td>
<td>78.0</td>
<td>79.1</td>
<td>78.5</td>
<td>78.3</td>
</tr>
</tbody>
</table>

*Median
## Baseline Concomitant Medications

<table>
<thead>
<tr>
<th>Subjects randomized</th>
<th>Placebo</th>
<th>Ustekinumab</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>130 mg</td>
<td>~6 mg/kg</td>
<td>Combined</td>
<td></td>
</tr>
<tr>
<td>Subjects with e1 medication, n (%)</td>
<td>185 (74.9)</td>
<td>178 (72.7)</td>
<td>174 (69.9)</td>
<td>352 (71.3)</td>
<td>537 (72.5)</td>
</tr>
<tr>
<td>Immunomodulators, n (%)</td>
<td>81 (32.8)</td>
<td>74 (30.2)</td>
<td>78 (31.3)</td>
<td>152 (30.8)</td>
<td>233 (31.4)</td>
</tr>
<tr>
<td>6-MP/AZA</td>
<td>58 (23.5)</td>
<td>52 (21.2)</td>
<td>56 (22.5)</td>
<td>108 (21.9)</td>
<td>166 (22.4)</td>
</tr>
<tr>
<td>MTX</td>
<td>24 (9.7)</td>
<td>22 (9.0)</td>
<td>22 (8.8)</td>
<td>44 (8.9)</td>
<td>68 (9.2)</td>
</tr>
<tr>
<td>Aminosalicylates, n (%)</td>
<td>54 (21.9)</td>
<td>50 (20.4)</td>
<td>50 (20.1)</td>
<td>100 (20.2)</td>
<td>154 (20.8)</td>
</tr>
<tr>
<td>Antibiotics, n (%)</td>
<td>21 (8.5)</td>
<td>19 (7.8)</td>
<td>24 (9.6)</td>
<td>43 (8.7)</td>
<td>64 (8.6)</td>
</tr>
<tr>
<td>Corticosteroids (including budesonide), n (%)</td>
<td>111 (44.9)</td>
<td>121 (49.4)</td>
<td>108 (43.4)</td>
<td>229 (46.4)</td>
<td>340 (45.9)</td>
</tr>
<tr>
<td>Pred-Eq Dose- mg* (n)</td>
<td>18.8 (89)</td>
<td>19.8 (108)</td>
<td>19.5 (88)</td>
<td>19.7 (196)</td>
<td>19.4 (285)</td>
</tr>
</tbody>
</table>

*Excluding budesonide (mean)
## TNF Antagonist Failure History

<table>
<thead>
<tr>
<th>Subjects randomized</th>
<th>Placebo 247</th>
<th>Ustekinumab</th>
<th>130 mg</th>
<th>~6 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with <strong>inadequate initial response</strong>, n (%)</td>
<td>74 (30.0)</td>
<td>70 (28.6)</td>
<td>72 (28.9)</td>
<td>216 (29.1)</td>
<td></td>
</tr>
<tr>
<td>Subjects with <strong>response followed by LOR</strong>, n (%)</td>
<td>170 (68.8)</td>
<td>173 (70.6)</td>
<td>171 (68.7)</td>
<td>514 (69.4)</td>
<td></td>
</tr>
<tr>
<td>Subjects with <strong>intolerance</strong>, n (%)</td>
<td>87 (35.2)</td>
<td>78 (31.8)</td>
<td>105 (42.2)</td>
<td>270 (36.4)</td>
<td></td>
</tr>
<tr>
<td>Subjects with inadequate initial αTNF response/LOR or intolerance, n (%) to:</td>
<td>246 (99.6)</td>
<td>243 (99.2)</td>
<td>246 (98.8)</td>
<td>735 (99.2)</td>
<td></td>
</tr>
<tr>
<td><strong>1 TNF antagonist</strong></td>
<td>112 (45.3)</td>
<td>124 (50.6)</td>
<td>120 (48.2)</td>
<td>356 (48.0)</td>
<td></td>
</tr>
<tr>
<td><strong>2 TNF antagonists</strong></td>
<td>108 (43.7)</td>
<td>92 (37.6)</td>
<td>102 (41.0)</td>
<td>302 (40.8)</td>
<td></td>
</tr>
<tr>
<td><strong>3 TNF antagonists</strong></td>
<td>26 (10.5)</td>
<td>27 (11.0)</td>
<td>24 (9.6)</td>
<td>77 (10.4)</td>
<td></td>
</tr>
</tbody>
</table>

LOR = loss of response

Primary Endpoint: Clinical Response at Week 6 (e100 Point CDAI Reduction)

Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to designated analysis time point are considered not to be in clinical response, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at designated analysis endpoint are considered not to be in clinical response.

*Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight ≤55 kg), 390 mg (weight >55 mg and ≤85 kg), 520 mg (weight >85 kg).

![Bar chart showing the proportion of subjects (%)](chart)

- Placebo (N=247): 21.5%
- 130 mg (N=245): 34.3%
- ~6 mg/kg* (N=249): 33.7%

p=0.002

p=0.003

Major Secondary Endpoint: Clinical Remission at Week 8 (CDAI < 150)

Randomized Subjects in Clinical Remission*,** at Week 8

- Placebo (N=247): 7.3%
- 130 mg (N=245): 15.9%
- ~6 mg/kg† (N=249): 20.9%

*Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to Week 8 are considered not to be in clinical remission, regardless of their CDAI score.

**Subjects who had insufficient data to calculate the CDAI score at Week 8 are considered not to be in clinical remission.

†Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight <55 kg), 390 mg (weight >55 mg and <85 kg), 520 mg (weight >85 kg).

Clinical Response Through Week 8

UNITI-1 & UNITI-2

UNITI-1
anti-TNF refractory

UNITI-2
failed prior conventional therapy (primarily anti-TNF naïve)

Proportion of Subjects (%)

Weeks

0 1 2 3 4 5 6 7 8

Proportion of Subjects (%)

Weeks

0 1 2 3 4 5 6 7 8

*Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight d55 kg), 390 mg (weight >55 mg and d85 kg), 520 mg (weight >85 kg).

Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to designated analysis time point are considered not to be in 70-point response, regardless of their CDAI score.

Subjects who had insufficient data to calculate the CDAI score at designated analysis endpoint are considered not to be in clinical response.

All p-values < 0.05

Clinical Remission Through Week 8

UNITI-1 & UNITI-2

UNITI-1
anti-TNF refractory

UNITI-2
failed prior conventional therapy (primarily anti-TNF naïve)

Proportion of Subjects (%)

Weeks

All p-values <0.05 except 130 mg dose at Week 3 in both studies

*Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight d55 kg), 390 mg (weight >55 mg and d85 kg), 520 mg (weight >85 kg).
Subjects who had a prohibited Crohn’s disease-related surgery or had prohibited concomitant medication changes prior to designated analysis time point are considered not to be in 70-point response, regardless of their CDAI score.
Subjects who had insufficient data to calculate the CDAI score at designated analysis endpoint are considered not to be in clinical remission.

Sandborn WJ et al. CCFA 2015
UNITI-1 & UNITI-2

70-Point Response Through Week 8

All p-values < 0.005

UNITI-1
anti-TNF refractory

UNITI-2
failed prior conventional therapy (primarily anti-TNF naïve)

Proportion of Subjects (%)

0 10 20 30 40 50 60 70 80

0 3 6 8

Weeks

All p-values < 0.005

UNITI-1
anti-TNF refractory

UNITI-2
failed prior conventional therapy (primarily anti-TNF naïve)

Proportion of Subjects (%)

0 10 20 30 40 50 60 70 80

0 3 6 8

Weeks

*Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight <55 kg), 390 mg (weight >55 mg and <85 kg), 520 mg (weight >85 kg).

Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to designated analysis time point are considered not to be in 70-point response, regardless of their CDAI score.

Subjects who had insufficient data to calculate the CDAI score at designated analysis endpoint are considered not to be in 70-point response.

Change in CRP Concentration Through Week 8

UNITI-1 & UNITI-2

UNITI-1
anti-TNF refractory

UNITI-2
failed prior conventional therapy
(primarily anti-TNF naïve)

All p-values < 0.001

Subjects who, prior to the designated analysis timepoint, had a prohibited Crohn’s disease-related surgery or had prohibited concomitant medication changes, had their baseline value carried forward.

Subjects who had insufficient data at the designated analysis timepoint had their last value carried forward.
Additional Efficacy Analyses

• Efficacy confirmed by significant improvements in change in CDAI and normalization of CRP at all study visits as well as in IBDQ and fecal lactoferrin/calprotectin at follow up assessments at Week 6
# Summary of Key Safety Events Through Week 8

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ustekinumab</th>
<th>Ustekinumab</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>130 mg</td>
<td>~6 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Treated subjects in induction phase</td>
<td>245</td>
<td>246</td>
<td>249</td>
<td>495</td>
</tr>
<tr>
<td>Avg. duration of follow-up (weeks)</td>
<td>7.9</td>
<td>7.9</td>
<td>7.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Subjects with e1, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE</td>
<td>159 (64.9)</td>
<td>159 (64.6)</td>
<td>164 (65.9)</td>
<td>323 (65.3)</td>
</tr>
<tr>
<td>SAE</td>
<td>15 (6.1)</td>
<td>12 (4.9)</td>
<td>18 (7.2)</td>
<td>30 (6.1)</td>
</tr>
<tr>
<td>Infection</td>
<td>58 (23.7)</td>
<td>57 (23.2)</td>
<td>64 (25.7)</td>
<td>121 (24.4)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>3 (1.2)</td>
<td>3 (1.2)</td>
<td>7 (2.8)</td>
<td>10 (2.0)</td>
</tr>
<tr>
<td>AEs temporally related to infusion</td>
<td>5 (2.0)</td>
<td>11 (4.5)</td>
<td>9 (3.6)</td>
<td>20 (4.0)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>0</td>
<td>0*</td>
<td>0</td>
</tr>
<tr>
<td>MACE**</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No anaphylaxis or serious infusion reactions reported

*Multiple myeloma following Week 20 safety f/u visit; **Major Adverse Cardiovascular Events

Conclusions

In moderately to severely active Crohn’s disease patients, previously failing one or more TNF-antagonists:

- IV ustekinumab significantly induced clinical response and clinical remission
- Magnitudes of treatment effects were greater at the higher ~6mg/kg dose than for the lower 130 mg induction dose, particularly at the final Week 8 induction endpoint
- Clinical Efficacy was confirmed by improvements in HRQOL and reductions in objective markers of inflammation
- Both IV ustekinumab induction regimens were well tolerated

Coupled with the previously reported UNITI-2 study results, induction efficacy with UST has been demonstrated across the moderately to severely active CD patient population, including Anti-TNF naïve and failure patients.