New Therapies on the Horizon

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IBD Pathogenesis

Neurath Nature Reviews. 2014
Cytokines in pathogenesis of IBD

Neurath Nature Reviews. 2014
Cytokine signaling in IBD

Neurath Nature Reviews. 2014
IL-12 and IL-23, their receptors and downstream signaling pathways

![Diagram showing IL-12 and IL-23 signaling pathways]

- IL-23
  - IL-23R
  - p19
  - p40
  - IL-12Rβ1
  - JAK2
  - STAT3
  - IL-17A, IL-17F, IL-22
  - TH17 stabilization

- IL-12
  - IL-12Rβ2
  - p35
  - p40
  - JAK2
  - STAT3
  - IFN-γ
  - TH1 development

Anti-P19 --- Ustekinumab

--- Ustekinumab

Teng Nature Med. 2015
Etrolizumab, anti-β7 mAb, Selectively Blocks T Cell Trafficking and Retention

# UNITI: Phase III UST Development Program in CD

## UNITI-1
Evaluate the safety/efficacy of ustekinumab induction therapy in subjects with moderately-to-severely active Crohn's disease who have **failed or are intolerant to aTNF therapy**

## UNITI-2
Evaluate the safety/efficacy of ustekinumab induction therapy in subjects with moderately-to-severely active Crohn's disease who have **failed or are intolerant to corticosteroids or immunosuppressants or are dependent on corticosteroid medications**

## IM-UNITI
Evaluate the safety/efficacy of ustekinumab **maintenance therapy in subjects with moderately-to-severely active Crohn’s disease that responded to induction**
UST Achieves Superior Clinical Outcomes after Single IV Dose in anti-TNF & Conventional Failures

UNITI-1

- aTNF Failures
- Primary Endpoint
- PBO (n = 247)
- UST 130 mg (n = 245)
- UST ~6 mg/kg (n = 249)

UNITI-2

- Conventional Failures
- Primary Endpoint
- PBO (n = 209)
- UST 130 mg (n = 209)
- UST ~6 mg/kg (n = 209)

- UNITI-1 (N=741): median CDAI ~317, CD dx ~10.1 yrs; all pts failed aTNF (1º or 2º LOR): 1+ (100%), 2+ (51%), 3 (10%)
- UNITI-2 (N = 628): median CDAI ~292 despite conv. therapy; CD dx ~6.4 yrs, CS (~39%), IS (~35%), aTNF-exposed (~31%)

UST SC Maintains Clinical Remission and Response

Clinical Outcomes at Week 52

- Phase III, multicentre, prospective RCT, N = 397 UST week 8 responders randomized from UNITI-1 and UNITI-2 induction trials
- Mod-to-sev CD (med. BL CDAI ~311), CD dx ~7.6 yrs, aTNF-refractory (~45%)

Rates of Clinical Outcomes Appear Higher in Bio-Naïve Patients

- Data sets suggest that absolute rates of clinical outcomes appear higher in bio-naïve pts
- Prior Bx exposure may be a marker for treatment resistant disease and may impact efficacy of subsequent therapy

UST Reduces Endoscopic Activity at Weeks 8 and 52

- Endoscopic sub-study of the prospective ph III RCTs UNITI-1, 2 & IM-UNITI
  - Endoscopies at wk 0, wk 8, and wk 52
  - Eligible subjects (aTNF-failures, experienced, bio-naïve included) must have lesions at wk 0
- Central reader blindly scored all video endoscopies and SES-CD

Rutgeerts et al. UEGW 2016, Abstract OP104
Proportion of patients with CD experiencing loss of response to ustekinumab maintenance therapy
**PSOLAR: Psoriasis Longitudinal Assessment and Registry**

**Cumulative Incidence Rates of Malignancy (Excluding NMSC) in PsO**

- **PSOLAR** is a multicentre observational registry of 12,093 PsO pts treated with all therapies, med f/u = ~3.4 yrs/pt, the overall prevalence of IBD is 2.3%
- **BL characteristics** were comparable, though IFX used in more sev PsO
- Events attributed to UST first, IFX second, all other Bx 3rd, then non-Bx
- Multivariate analyses: UST is not associated with increased risk of malignancy, major adverse CV events, serious infections or mortality
Incidence of Serious Infections in patients with PsO and prevalent IBD

Rates of Serious Infections per 100 PY*

- PSOLAR is a multicentre observational registry of 12,093 PsO pts treated with all therapies, med f/u = ~3.4 yrs/pt, the overall prevalence of IBD is 2.3%
- BL characteristics were comparable, though IFX used in more sev PsO
- Events attributed to UST first, IFX second, all other Bx 3rd, then non-Bx
The Race to Develop IL 23 (p19) Antibodies

- **Brazikumab** (AstraZeneca/Medimmune/Amgen, now Allergan)
- **Risankizumab** (Boehringer Ingelheim, now Abbvie)
- **Geslekumab** (Janssen)
- **LY3074828** (Lilly)
- **MK 3222** (Merck)
Binding of cytokine receptors by cytokines activates JAK pathways signaling

1. Cytokine binding to its cell surface receptor leads to receptor polymerization and activation of associated JAKs.

2. Activated JAKs phosphorylate the receptors that dock STATs.

3. Activated JAKs phosphorylate STATs, which dimerize and move to the nucleus to activate new gene transcription.
Consequence of Janus kinase (JAK) inhibition on signaling by key immunoregulatory cytokines

Tofactinib Jak 1>3
Filgotinib/
Upadacitinib Jak 1

Tofacitinib an oral JAK inhibitor

- Inhibits JAK1, JAK2, and JAK3 in vitro
- Functional cellular specificity for JAK1 and JAK3 over JAK2
- Modulates signaling for an important subset of pro-inflammatory cytokines including IL-2, -4, -7, -9, -15, and -21

Phase 3 Program Design

Patients

- ≥18 years old, moderately to severely active ulcerative colitis (Mayo score ≥6; rectal bleeding subscore ≥1; centrally read endoscopic subscore ≥2 (colonoscopy or flexible sigmoidoscopy)
- Prior failure or intolerance to ≥1 of: corticosteroids, azathioprine, 6-MP or TNF inhibitors (TNFi)
- Washout: TNFi, 8 weeks; immunosuppressants, 2 weeks
- Concomitant corticosteroids: max dose 25 mg/day; stable during the study
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>OCTAVE Induction 1</th>
<th>OCTAVE Induction 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=122</td>
<td>Tofacitinib 10 mg BID N=476</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>36.9</td>
<td>41.8</td>
</tr>
<tr>
<td>Age, years(^a)</td>
<td>41.8 (15.3)</td>
<td>41.3 (14.1)</td>
</tr>
<tr>
<td>Geographic region, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>59.0</td>
<td>59.9</td>
</tr>
<tr>
<td>North America</td>
<td>24.6</td>
<td>21.4</td>
</tr>
<tr>
<td>Other</td>
<td>16.4</td>
<td>18.7</td>
</tr>
<tr>
<td>Disease duration, years(^a)</td>
<td>8.4 (7.6)</td>
<td>8.3 (7.1)</td>
</tr>
<tr>
<td>Total Mayo score(^a)</td>
<td>9.1 (1.4)</td>
<td>9.0 (1.4)</td>
</tr>
<tr>
<td>Extent of disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctosigmoiditis</td>
<td>15.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>30.3</td>
<td>33.3</td>
</tr>
<tr>
<td>Extensive colitis or pancolitis</td>
<td>54.1</td>
<td>53.1</td>
</tr>
<tr>
<td>Prior TNFi treatment, %</td>
<td>53.3</td>
<td>53.4</td>
</tr>
<tr>
<td>Prior TNFi failure, %</td>
<td>52.5</td>
<td>51.1</td>
</tr>
<tr>
<td>Prior immunosuppressant failure, %</td>
<td>68.0</td>
<td>75.6</td>
</tr>
<tr>
<td>Prior corticosteroid failure, %</td>
<td>80.3</td>
<td>73.5</td>
</tr>
<tr>
<td>Oral corticosteroid use, %</td>
<td>47.5</td>
<td>45.0</td>
</tr>
</tbody>
</table>

\(^a\)Mean (standard deviation)
Tofacitinib Efficacy by TNF inhibitor exposure

**OCTAVE Induction 1**

- **Remission**
  - Yes: 1.5, 12.6, 15.8, 25.2
  - No: 0, 20, 40, 60
  - Change: ∆=11.1
  - Percentage of patients with remission:
    - Prior TNF exposure
      - Yes: 26.3
      - No: 42.4

- **Mucosal healing**
  - Yes: 6.2, 24.0, 26.3, 39.6
  - No: 0, 20, 40, 60
  - Change: ∆=17.9
  - Percentage of patients with mucosal healing:
    - Prior TNF exposure
      - Yes: 21.8
      - No: 48.0

**OCTAVE Induction 2**

- **Remission**
  - Yes: 0, 12.0, 8.5, 22.1
  - No: 0, 20, 40, 60
  - Change: ∆=12.0
  - Percentage of patients with remission:
    - Prior TNF exposure
      - Yes: 24.0
      - No: 50.5

- **Mucosal healing**
  - Yes: 6.2, 21.8, 19.1, 36.4
  - No: 0, 20, 40, 60
  - Change: ∆=15.6
  - Percentage of patients with mucosal healing:
    - Prior TNF exposure
      - Yes: 21.8
      - No: 48.0

Mucosal healing

- Placebo: 13.1%
- Tofacitinib 5 mg BID: 37.4% (p<0.001 vs Placebo, Δ=24.2)
- Tofacitinib 10 mg BID: 45.7% (p<0.001 vs Placebo, Δ=32.6)

Proportion of patients (%)

<table>
<thead>
<tr>
<th>n/N</th>
<th>Diff. from placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26/198</td>
<td>- (95% CI)</td>
</tr>
</tbody>
</table>

Sustained Corticosteroid-free Remission

Sustained steroid-free remission at Weeks 24 & 52, among remitters at baseline

<table>
<thead>
<tr>
<th>n/N</th>
<th>Diff. from placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/59</td>
<td>-</td>
</tr>
<tr>
<td>23/65</td>
<td>30.3 (17.4, 43.2)</td>
</tr>
<tr>
<td>26/55</td>
<td>42.2 (27.9, 56.5)</td>
</tr>
</tbody>
</table>

Proportion of patients (%)

- Placebo: 5.1
- Tofacitinib 5 mg BID: 35.4
- Tofacitinib 10 mg BID: 47.3

p < 0.001
Results of the OCTAVE maintenance trial of tofacitinib in ulcerative colitis

Efficacy and safety of oral tofacitinib as maintenance therapy in patients with ulcerative colitis: Results from a phase 3 randomized controlled trial. DDW. 2017:1080
Incidence rates of herpes zoster and herpes simplex associated with anti-TNF and tofacitinib in RA

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Person-Years</th>
<th>Incidence Rate*</th>
<th>Adjusted HR(^{\text{b}}) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>330</td>
<td>6832.8</td>
<td>4.83 (4.34-5.38)</td>
<td>0.89 (0.77-1.03)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>161</td>
<td>2940.7</td>
<td>5.47 (4.69-6.39)</td>
<td>1.00 (0.83-1.19)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>89</td>
<td>1670.8</td>
<td>5.33 (4.33-6.56)</td>
<td>1.01 (0.80-1.27)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>492</td>
<td>8201.4</td>
<td>6.00 (5.49-6.55)</td>
<td>1.06 (0.93-1.21)</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>74</td>
<td>972.9</td>
<td>7.61 (6.06-9.55)</td>
<td>1.40 (1.09-1.81)</td>
</tr>
</tbody>
</table>

*Per 100 person-years.

\(^{\text{b}}\)Adjusted for age, sex, baseline glucocorticoid use, methotrexate, number of biologics used, hospitalization, hospitalized infection, outpatient infection and zoster vaccination.

### Summary of adverse events

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tofacitinib 5 mg BID</th>
<th>Tofacitinib 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events, n (%)</strong></td>
<td>149 (75.3)</td>
<td>143 (72.2)</td>
<td>156 (79.6)</td>
</tr>
<tr>
<td><strong>Most frequently occurring adverse events by preferred term (≥8%), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening ulcerative colitis</td>
<td>71 (35.9)</td>
<td>36 (18.2)</td>
<td>29 (14.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11 (5.6)</td>
<td>19 (9.6)</td>
<td>27 (13.8)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>19 (9.6)</td>
<td>17 (8.6)</td>
<td>17 (8.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (6.1)</td>
<td>17 (8.6)</td>
<td>6 (3.1)</td>
</tr>
<tr>
<td><strong>Serious adverse events, n (%)</strong></td>
<td>13 (6.6)</td>
<td>10 (5.1)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td><strong>Discontinuations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to adverse events, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>37 (18.7)</td>
<td>18 (9.1)</td>
<td>19 (9.7)</td>
</tr>
<tr>
<td><strong>Insufficient clinical response, n (%)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>132 (66.7)</td>
<td>70 (35.4)</td>
<td>53 (27.0)</td>
</tr>
<tr>
<td>Safety events of special interest</td>
<td>Placebo N=198</td>
<td>Tofacitinib 5 mg BID N=198</td>
<td>Tofacitinib 10 mg BID N=197</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Infections, n (%)</td>
<td>48 (24.2)</td>
<td>71 (35.9)</td>
<td>78 (39.8)</td>
</tr>
<tr>
<td>Serious infections, n (%)(^a)</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>
| Herpes zoster, n (%)
  All cases\(^b\)     | 1 (0.5)       | 3 (1.5)                  | 10 (5.1)                  |
| Multidermatomal (non-adjacent or >2 adjacent dermatomes)\(^c\) | 1 (0.5)       | 2 (1.0)                  | 4 (2.0)                   |
| Disseminated\(^c\)               | 1 (0.5)       | 0 (0)                    | 0 (0)                     |
| Cardiovascular events, n (%)\(^d\) | 0 (0.0)       | 1 (0.5)\(^e\)           | 1 (0.5)\(^f\)            |
| Intestinal perforations, n (%)\(^d,g\) | 1 (0.5)\(^h\) | 0 (0.0)                  | 0 (0.0)                   |
| Malignancies, excluding NMSC, n (%)\(^d\) | 1 (0.5)\(^i\) | 0 (0.0)                  | 0 (0.0)                   |
| NMSC                              | 1 (0.5)       | 0 (0.0)                  | 3 (1.5)                   |
| Death                             | 0 (0)         | 0 (0)                    | 0 (0)                     |
Efficacy and Safety of Tofacitinib in Crohn’s Disease

8-Week Induction Study (N = 280)

- **Primary Endpoint**
  - Remission wk 8:
    - PBO: 37%
    - Tofa 5 mg BID: 44%
    - Tofa 10 mg BID: 43%
  - CR-100:
    - PBO: 91%
    - Tofa 5 mg BID: 54%
    - Tofa 10 mg BID: 71%

- aTNF-experienced (68%); CR: Clinical Response; *p<0.05

Panes et al. ECCO 2016, Abstract OP022
Efficacy and Safety of Filgotinib in Mod-Sev CD

Remission and Response Week 10 (N=275)

Primary Endpoint

<table>
<thead>
<tr>
<th>Remission</th>
<th>CR-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>23</td>
</tr>
<tr>
<td>200 mg FGN</td>
<td>48 *</td>
</tr>
<tr>
<td>10/44</td>
<td>18/44</td>
</tr>
<tr>
<td>61/128</td>
<td>77/128</td>
</tr>
</tbody>
</table>

Change in IBDQ at Week 10

<table>
<thead>
<tr>
<th>∆ in IBDQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
</tr>
<tr>
<td>34 **</td>
</tr>
</tbody>
</table>

aTNF-experienced (68%); CR: Clinical Response; *p<0.05; **p<0.01

Vermeire et al. ECCO 2016, Abstract OP020
Modulation of S1P Receptors Results in Retention of Lymphocyte Subsets (CCR7^+ ) in the Lymph Node

- Lymphocyte subsets (CCR7^+ ) circulate through lymph nodes
- Exit of these lymphocytes from the lymph node is S1P_1R dependent
- Ozanimod down modulates S1P_1R, preventing these lymphocytes from exiting and contributing to tissue inflammation
- Lymphocytes subsets (CCR7^- ) important for viral and tumor surveillance continue to circulate
Ozanimod: Study Design

**Induction Period**

- Placebo (N=65)
- Ozanimod 0.5 mg (N=65)
- Ozanimod 1 mg (N=67)

**Primary Endpoint: Induction**

**Maintenance Period**

- 24 Weeks Treatment
- Week 32 Maintenance Endpoint

**Randomization**

1 Week Initial Doses

8 Weeks Treatment

Mayo Responders

Disease Relapse

Non-Responders

Open-Label Ozanimod 1 mg
Clinical Remission* at Week 8 and Week 32

*Clinical remission defined as a Mayo Clinic Score ≤2, with no individual subscore >1 point