Biologics and Beyond in IBD Therapy

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Disclosures

• Consultant: Janssen Biotech, Abbvie, Takeda

• Speaker’s Bureau: Janssen Biotech, Abbvie, Takeda
The problem with anti-TNFS: Infliximab discontinuation due to treatment failure

Potential adverse effects of anti-TNF

- Autoimmunity, immunogenicity
- Congestive heart failure
- Demyelinating disease (e.g. multiple sclerosis)
- Hepatotoxicity
- Bone marrow suppression
- Infusion reactions, injection-site reactions
- Skin cancers, Lymphoma
  - Sun protection
  - Dermatology exams
  - Routine follow-up
- Infection - Impact of vaccinations

PML, progressive multifocal leukoencephalopathy
New Mechanisms of Action for IBD Treatment

- Anti-Trafficking
- Anti-Adhesion
- Anti-Cytokine
- JAK/STAT
- Fecal Microbiota Transplant (FMT)
Anti-Trafficking: S1P1R modulation results in sequestration of select lymphocyte subsets

- T-Cells expand and mature in the lymph nodes after being activated by gut bacteria
- S1P$_{1R}$ modulators induce S1P$_{1R}$ internalization so T-Cells are locked from leaving the lymph node
- Trapping lymphocytes at the earliest stage of trafficking blocks downstream inflammation
- Protective immunity is generally preserved by effector memory T cells that do not circulate through the lymph nodes
- Ozanimod (RCP1063) is a next generation oral S1P receptor
- Phase 3 UC and Phase 2 Crohn’s

Ozanimod Phase 2 in Ulcerative Colitis (TOUCHSTONE study): Week 8 endpoints

Primary Endpoint

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo 65</th>
<th>Ozanimod 0.5 mg 65</th>
<th>Ozanimod 1 mg 67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (%)</td>
<td>6.2</td>
<td>13.8</td>
<td>16.4</td>
</tr>
<tr>
<td>Response (%)</td>
<td>37</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>Mucosal healing (%)</td>
<td>12</td>
<td>28</td>
<td>34</td>
</tr>
</tbody>
</table>

*p-values: p=0.1422, p=0.0648, p=0.0482, p=0.0140, p=0.0348, p=0.0023

Ozanimod Phase 2 in Ulcerative Colitis (TOUCHSTONE study): Week 32 endpoints

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

### Patients (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Ozanimod 0.5 mg</th>
<th>Ozanimod 1 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>6.2</td>
<td>26.2</td>
<td>32.6</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td>20.8</td>
<td>32.8</td>
</tr>
<tr>
<td>Mucosal healing</td>
<td></td>
<td>20</td>
<td>12.9</td>
</tr>
<tr>
<td>(Mayo endo-subscore ≤1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p = 0.0021, p = 0.0108, p = 0.0571, p = 0.0002, p = 0.0044, p = 0.0044

Anti-Adhesion: Integrins are essential for the entry of immune cells into inflamed tissues

Torres J et al. Lancet, in press
Vedolizumab targets the colon
Vedolizumab blocks the interaction between α4β7 and MAdCAM-1
GEMINI I: Vedolizumab in UC Efficacy at week 6 (induction)

![Graph showing clinical response, remission, and mucosal healing with placebo and vedolizumab groups.](Image)

- **Clinical Response**:
  - Placebo: 25.5%
  - Vedolizumab: 47.1%
  - Difference: Δ 21.7
  - 95% CI: 11.6, 31.7
  - *P* < 0.0001

- **Clinical Remission**:
  - Placebo: 5.4%
  - Vedolizumab: 16.9%
  - Difference: Δ 11.5
  - 95% CI: 4.7, 18.3
  - *P* = 0.0009

- **Mucosal Healing**:
  - Placebo: 24.8%
  - Vedolizumab: 40.9%
  - Difference: Δ 16.1
  - 95% CI: 6.4, 25.9
  - *P* = 0.0012

GEMINI I: Vedolizumab In UC Primary and secondary outcomes through 52 Weeks, maintenance ITT population


*P<0.05  **P<0.01  ***P<0.0001
Anti-Cytokine Therapy

Torres J et al. Lancet, in press
Ustekinumab (Stelara) Background

- Ustekinumab is a fully human IgG1k monoclonal antibody that binds the p40 subunit of Interleukins-12 & 23
- Approved for psoriasis and psoriatic arthritis
- FDA approval for Crohn’s disease expected in next few months

![Diagram showing the interaction of Ustekinumab with IL-12 and IL-23](image)

No IL-12 or IL-23
Intracellular signal
## UNITI-1

### Results:
- Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized</td>
<td>741</td>
</tr>
<tr>
<td>CDAI score*</td>
<td>317</td>
</tr>
<tr>
<td>C-reactive protein*</td>
<td>9.9 mg/L</td>
</tr>
<tr>
<td>CD duration (years)*</td>
<td>10.1</td>
</tr>
<tr>
<td>Previously failed ≥2 anti-TNFs</td>
<td>51%</td>
</tr>
<tr>
<td>Primary non-response</td>
<td>29.1%</td>
</tr>
<tr>
<td>Secondary non-response</td>
<td>69.4%</td>
</tr>
<tr>
<td>Intolerance to at least one TNF antagonist</td>
<td>36.4%</td>
</tr>
</tbody>
</table>

* Median

UNITI – 1: Clinical Response at Week 6

Proportion of Subjects (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>21.5 %</td>
</tr>
<tr>
<td>Ustekinumab 130 mg</td>
<td>34.3 %</td>
</tr>
<tr>
<td>Ustekinumab ~6 mg/kg</td>
<td>33.7 %</td>
</tr>
</tbody>
</table>

UNITI – 1

Secondary Endpoint:
Randomized Subjects in Clinical Response* and Clinical Remission* at Week 8

<table>
<thead>
<tr>
<th></th>
<th>Clinical Response</th>
<th>Clinical Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20.2 %</td>
<td>7.3 %</td>
</tr>
<tr>
<td>130 mg</td>
<td>33.5 %</td>
<td>15.9 %</td>
</tr>
<tr>
<td>~ 6 mg/kg</td>
<td>37.8 %</td>
<td>20.9 %</td>
</tr>
</tbody>
</table>

p≤0.001          p≤0.001          p=0.003          p<0.001

Ustekinumab

## Results:

- Baseline Demographics, Disease Characteristics and Concomitant Medications

<table>
<thead>
<tr>
<th>Medical Parameter</th>
<th>Percentage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized</td>
<td></td>
<td>628</td>
</tr>
<tr>
<td>CDAI score*</td>
<td></td>
<td>303</td>
</tr>
<tr>
<td>CD duration (years)*</td>
<td></td>
<td>6.40</td>
</tr>
<tr>
<td>Corticosteroids (including budesonide), %</td>
<td></td>
<td>39%</td>
</tr>
<tr>
<td>Immunomodulators, %</td>
<td></td>
<td>35%</td>
</tr>
<tr>
<td>TNF-antagonist naïve, %</td>
<td></td>
<td>69%</td>
</tr>
<tr>
<td>Previously treated with anti-TNFs but did not fail therapy, %</td>
<td></td>
<td>31%</td>
</tr>
</tbody>
</table>

* Median

UNITI-2

Primary Endpoint: Clinical Response at Week 6 (≥100 Point CDAI Reduction)

- Placebo (N=209): 28.7%
- 130 mg (N=209): 51.7%
  - p<0.001, Δ 23.0%
- ~6 mg/kg* (N=209): 55.5%
  - p<0.001, Δ 26.8%
- Combined (N=418): 53.6%
  - p<0.001, Δ 24.9%

p=0.001
UNITI-2

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

- Placebo (N=209): 19.6%
- 130 mg (N=209): 30.6%, p=0.009, Δ 11.0%
- ~6 mg/kg * (N=209): 40.2%, p<0.001, Δ 20.6%
- Combined (N=418): 35.4%, p<0.001, Δ 15.8%

Ustekinumab: Safety

- Rates of AE and SAE were similar among placebo and drug
- One opportunistic infection reported in the UST 6mg/kg group – Listeria meningitis
- No malignancies or death
Selective IL-23 Blockade with Risankizumab Shows Promise in Moderate-to-Severe CD

Background
- Risankizumab is an anti-p19 antibody, thereby selectively blocking IL-23
- Risankizumab was superior to ustekinumab in a head-to-head psoriasis trial

Methods
- Phase 2, placebo-controlled, double-blind, 12-week induction trial
- Endoscopies at baseline and at week 12 assessed by blinded central reader
- 94.2% were anti-TNF experienced; 56-59% had >2 prior anti-TNFs

Results
- Efficacy (primary endpoint):

  - Clinical Remission at Week 12
    - Placebo (n=89): 15.4%
    - 200 mg (n=41): 24.4%
    - 600 mg (n=41): 36.6%
    - Pooled risankizumab (n=82): 30.5% * p < 0.05 compared to placebo

  - Endoscopic Remission at Week 12
    - Placebo (n=89): 2.6%
    - 200 mg (n=41): 14.6%
    - 600 mg (n=41): 19.5%
    - Pooled risankizumab (n=82): 17.1% *

- Safety: Fewer serious AEs with risankizumab than with placebo

Potential Advantages of Small Molecule Therapies

• Reach optimal concentrations faster than other biologics
• Less risk of immunogenicity
• Less likely to need concomitant immunosuppressive therapy
### A Primary End Point

<table>
<thead>
<tr>
<th>Patients in Clinical Remission (%)</th>
<th>Placebo</th>
<th>10</th>
<th>12</th>
<th>55</th>
<th>65</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mongersen (mg/day)</strong></td>
<td></td>
<td>10</td>
<td>40</td>
<td>160</td>
<td></td>
</tr>
</tbody>
</table>

**No. of Patients**

<table>
<thead>
<tr>
<th>CDAI ≥150</th>
<th>Placebo</th>
<th>38</th>
<th>36</th>
<th>18</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI &lt;150</td>
<td>Placebo</td>
<td>4</td>
<td>5</td>
<td>22</td>
<td>28</td>
</tr>
</tbody>
</table>

### B Secondary End Point, Day 15 vs. Baseline

<table>
<thead>
<tr>
<th>Patients with Clinical Response (%)</th>
<th>Placebo</th>
<th>10</th>
<th>40</th>
<th>160</th>
<th></th>
</tr>
</thead>
</table>

**P**

- **P<0.001**
- **P=0.03**

### C Secondary End Point, Day 28 vs. Baseline

<table>
<thead>
<tr>
<th>Patients with Clinical Response (%)</th>
<th>Placebo</th>
<th>10</th>
<th>40</th>
<th>160</th>
<th></th>
</tr>
</thead>
</table>

**P**

- **P<0.001**
- **P=0.04**

Post Hoc Analysis - Mongersen

**Disease duration <5 Years**

- Week 2: Placebo 31.0, Mongersen 40 mg/day 68.0, Mongersen 10 mg/day 63.6
- Week 4: Placebo 25.0, Mongersen 40 mg/day 74.0, Mongersen 10 mg/day 63.2
- Week 12: Placebo 25.0, Mongersen 40 mg/day 79.0, Mongersen 10 mg/day 63.2

**Disease duration ≥5 Years**

- Week 2: Placebo 15.4, Mongersen 40 mg/day 10.3, Mongersen 160 mg/day 62.5
- Week 4: Placebo 15.4, Mongersen 40 mg/day 34.5, Mongersen 160 mg/day 70.6
- Week 12: Placebo 19.2, Mongersen 40 mg/day 31.0, Mongersen 160 mg/day 71.0

Post Hoc Analysis - Mongersen

(a) CDAI Score ≤ 260

(b) CDAI Score > 260

Mongersen: Safety

• **Serious Adverse Events**
  – Similar rates between placebo and drug
  – 9 serious adverse events in 6 patients
  – Most were hospitalization for Crohn’s flares
  – Others were fevers

• **Adverse Events**
  – Similar rates between placebo and drug
  – Abdominal pain, diarrhea, fever, flu like illness
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

JAK=Janus kinase; P=phosphate; STAT=signal transducer and activator of transcription.
Consequence of JAK Inhibition on Signaling by Key Immunoregulatory Cytokines

O’Shea J. Immunity 2012
Tofacitinib (CP-690,550) an Oral Janus Kinase (JAK) Inhibitor

- Inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular specificity for JAK1 and JAK3 over JAK2
- Directly or indirectly modulates signaling for an important subset of pro-inflammatory cytokines including IL-2, -4, -7, -9, -15, and -21

OCTAVE: Study design for Tofacitinib in UC

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

6-MP, 6-mercaptopurine; TNF, tumour necrosis factor
Primary endpoint: remission at Week 8

Data are full analysis set with non-responder imputation and based on centrally-read endoscopy. Significance vs placebo calculated by Cochran-Mantel-Haenszel chi-square test.
Key secondary endpoint: Mucosal healing at Week 8

Data are full analysis set with non-responder imputation and based on centrally-read endoscopy.
Significance vs placebo calculated by Cochran-Mantel-Haenszel chi-square test.
Efficacy by TNF inhibitor exposure

**OCTAVE Induction 1**

- **Percent of patients with remission**
  - Yes: 1.5, 12.6, 15.8, 25.2
  - No: 0, 20, 40, 60

- **Percent of patients with mucosal healing**
  - Yes: 6.2, 24.0, 26.3, 39.6
  - No: 0, 20, 40, 60

**OCTAVE Induction 2**

- **Percent of patients with remission**
  - Yes: 0, 12.0, 8.5, 22.1
  - No: 0, 20, 40, 60

- **Percent of patients with mucosal healing**
  - Yes: 6.2, 21.8, 19.1, 36.4
  - No: 0, 20, 40, 60

Data are full analysis set with non-responder imputation and based on centrally-read endoscopy.

*Placebo*  *Tofacitinib 10 mg BID*
<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>Adverse events, n (%)</td>
<td>73 (59.8%)</td>
<td>269 (56.5%)</td>
</tr>
<tr>
<td>Most frequently occurring adverse events by preferred term, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10 (8.2%)</td>
<td>37 (7.8%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9 (7.4%)</td>
<td>39 (8.2%)</td>
</tr>
<tr>
<td>Serious adverse events, n (%)</td>
<td>5 (4.1%)</td>
<td>16 (3.4%)</td>
</tr>
<tr>
<td>Discontinuations due to adverse events, n (%)</td>
<td>2 (1.6%)</td>
<td>18 (3.8%)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

*aDissecting aortic aneurysm; died on Study Day 31: This subject was a 40-year-old white male (Ukraine) without relevant past medical history or known risk factors for aortic dissection. Autopsy confirmed aortic aneurysm dissection and cardiac tamponade. The event was assessed as not related to study drug by the investigator.*
### Safety events of special interest

<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><strong>Infections, n (%)</strong></td>
<td>19 (15.6%)</td>
<td>111 (23.3%)</td>
</tr>
<tr>
<td><strong>Herpes zoster</strong></td>
<td>1 (0.8%)</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td><strong>Opportunistic infections</strong></td>
<td>0 (0.0%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td><strong>Serious infections, n (%)</strong></td>
<td>0 (0.0%)</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td><strong>Cardiovascular events, n (%)</strong></td>
<td>0 (0.0%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td><strong>Intestinal perforations, n (%)</strong></td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td><strong>Malignancies, n (%)</strong></td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td><strong>Non-melanoma skin cancer</strong></td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

- **a**There were no cases of tuberculosis in either study; **b**None were reported as serious adverse events; **c**Per an external independent adjudication committee based on pre-defined adjudication criteria; **d**One case of cytomegalovirus colitis; 3 cases herpes zoster (1 case: 2 adjacent dermatomes; 1 case: 2 or 3 non-adjacent dermatomes; 1 case >2 dermatomes); **e**Serious infections were: anal abscess, cellulitis, *clostridium difficile* infection, febrile infection, otitis externa, pneumonia, furuncle, all n=1
Tofacitinib Is Not Different From Placebo in Induction/Maintenance Therapy for CD

Methods
- Multicenter phase 2b study of induction and maintenance therapy for moderate-to-severe CD
- Randomized to placebo, tofacitinib 5 mg BID, or tofacitinib 10 mg BID
- Primary endpoint: clinical response/remission at weeks 8 and 26
- Secondary endpoints: clinical response; changes in CDAI, CRP, and fecal calprotectin over time

Results
- Compared to placebo, tofacitinib did not significantly increase clinical remission for induction
- Tofacitinib 10 mg BID had a higher proportion of patients maintaining clinical response, but no significant difference vs placebo

Filgotinib Is Safe and Effective for Treatment of Moderate-to-Severe CD

Methods

- Filgotinib is a selective once-daily oral JAK1 inhibitor
- The FITZROY study included 174 patients randomized to filgotinib 200 mg QD or placebo for 10 weeks
- All immunosuppressants discontinued
- Primary endpoint: CDAI <150 at 10 weeks
- Endoscopic data not yet presented

Results

![Bar chart showing percent responders for Placebo and Tofacitinib for Remission (CDAI <150) and Response (CDAI Reduction).](chart.png)

Conclusions

- Filgotinib has efficacy in moderate-to-severe CD patients
- During 10 weeks of treatment filgotinib was well tolerated; no unexpected safety findings