Optimizing Management of IBD: Beyond Anti-TNFs

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Disclosures: R. Panaccione


- **Speaker’s fees for:** Abbvie, Aptalis, AstraZeneca, Ferring, Janssen, Merck, Prometheus, Shire, Takeda

- **Advisory Board for:** Abbvie, Abbott, Amgen, Aptalis, AstraZeneca, Baxter, Biogen Idec, Eisai, Ferring, Genentech, Janssen, Merck, Shire, Elan, Glaxo-Smith Kline, Hospira, Pfizer, Bristol-Myers Squibb, Takeda, Cubist, Celgene, Salix

- **Research/Educational Support from:** Abbvie, Ferring, Janssen, Shire Takeda
Objectives

1. Discuss new treatment targets in IBD
   - Where we were
   - Where we are
   - Where we are going

2. Review the latest data that will impact your clinical practice in 2016 and beyond

3. Discuss positioning of new therapies in IBD
Managing IBD in 2016: An evolution in IBD care

Crohn’s disease (CD)

5-ASA Steroids
Azathioprine

Anti-TNFs for CD
Initial report

Anti-TNFs for CD

5-ASA Steroids
Azathioprine, Cyclosporin

Anti-TNFs for UC

Vedolizumab for UC

Biosimilars

1995

2000

2005

2010

2015/16

Ulcerative Colitis (UC)

5-ASA Steroids
Azathioprine

Anti-TNFs for CD

Surgery

Vedolizumab for CD

4. National Institute for Health and Care Excellence technology appraisal guidance [TA329]: Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262):
Introducing Biological Therapy: Where we were

- The biologic revolution began over 15 years ago with the approval of infliximab for the treatment of moderate to severe CD\(^1\).

- Despite the development and approval of “newer” anti TNFs, the overall induction of remission in RCTs was $\sim30\text{-}50\%^{2-5}$ and maintenance of remission was $\sim20\text{-}40\%^{6-10}$

- Therefore there is a need to develop new agents for the treatment of IBD.


Where we are: Lessons learned during the anti-TNF era

- Anti-TNFs are safe
- Antibodies are bad; adequate drug levels are good
- There is value in combination therapy
- Treating early is better
- We can treat beyond symptoms
- We can decrease surgical/hospitalization rates
- We do better in real life than in clinical trials
Phenotypic features of Crohn's disease associated with anti-TNF treatment failure

Retrospective study using the Alberta Inflammatory Bowel Disease Consortium registry. Probability of surgery over time after anti-TNF prescription depending on phenotype at prescription (B1=inflammatory, B2=stricturing, B2L1=ileal stricturing, B3=penetrating)
Randomised Evaluation of an Algorithm for Crohn’s Treatment (REACT 1)

Symptomatic remission (HBI≤4 and no corticosteroids)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Conventional management</th>
<th>Early combined immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>Month 6</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Month 12</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Month 18</td>
<td>30%</td>
<td>60%</td>
</tr>
<tr>
<td>Month 24</td>
<td>20%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Time to first hospitalisation, surgery or complication

HR (95% CI) = 0.73 (0.62, 0.86), p<0.001

34.7% vs 27.4%

REACT cluster randomisation:
898 CD in conventional management vs 1094 CD in early combined immunosuppression
Temporal trend analysis of colectomy rates: stratified by emergent vs. elective colectomy

Colectomy rates in adults hospitalised for a flare of UC

UC, ulcerative colitis.
Temporal changes were evaluated using linear regression models to estimate the average annual percent change (AAPC) in surgical rates.

Real Life vs. Clinical Trials: The example of ADA and IFX in UC

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>P-value</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding* n (%)</td>
<td>ADA n = 380</td>
<td>IFX n = 424</td>
<td>.5359</td>
<td>ADA n = 380</td>
<td>IFX n = 424</td>
<td>.0318</td>
</tr>
<tr>
<td>Abdominal pain/tenderness, n (%)</td>
<td>363 (95.3)</td>
<td>401 (94.6)</td>
<td>.5571</td>
<td>85 (22.4)</td>
<td>125 (29.0)</td>
<td>.6816</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>107 (28.2)</td>
<td>140 (33.4)</td>
<td>.0557</td>
<td>9 (2.4)</td>
<td>6 (1.2)</td>
<td>.9191</td>
</tr>
<tr>
<td>Weight loss</td>
<td>100 (26.9)</td>
<td>224 (53.6)</td>
<td>.0013</td>
<td>12 (3.2)</td>
<td>12 (2.8)</td>
<td>.4963</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>268 (70.5)</td>
<td>235 (56.0)</td>
<td>.7689</td>
<td>24 (6.3)</td>
<td>23 (5.8)</td>
<td>.4103</td>
</tr>
<tr>
<td>Presence of mucus</td>
<td>259 (68.3)</td>
<td>279 (65.1)</td>
<td>.1974</td>
<td>14 (3.7)</td>
<td>14 (3.4)</td>
<td>.7609</td>
</tr>
<tr>
<td>Any urgency of defecation</td>
<td>348 (91.4)</td>
<td>373 (86.0)</td>
<td>.0933</td>
<td>50 (13.5)</td>
<td>43 (10.0)</td>
<td>.2236</td>
</tr>
<tr>
<td>Increased stool frequency, n (%)</td>
<td>374 (98.4)</td>
<td>402 (95.5)</td>
<td>.0821</td>
<td>146 (39.0)</td>
<td>161 (42.7)</td>
<td>.2014</td>
</tr>
</tbody>
</table>

PGA, n (%)
- Normal: 1 (0.3) 6 (1.3)
- Mild: 20 (5.3) 25 (5.9)
- Moderate: 250 (61.1) 237 (56.0)
- Severe: 118 (31.1) 152 (35.6)
- Partial Mayo score, mean (SD): 6.3 (1.7) 6.4 (1.3)

*P-values were calculated using Wilcoxon rank-sum tests for continuous variables.

**Rectal bleeding was defined as “any blood seen” vs “no blood seen.”
Many biologic agents have failed in IBD

- **Anti-IL-2 receptor**
  - Basiliximab\(^1\)
  - Daclizumab\(^2\)

- **Anti-CTLA-4**
  - Abatacept\(^3\)

- **Anti-CD3 receptor**
  - Visilizumab\(^4\)

The IBD therapeutic pipeline

Adapted from Danese S. *Gut* 2012;61:918–32.
Emerging therapies in IBD

- Leukocyte Trafficking inhibitors
  - Vedolizumab
  - Etrolizumab
  - Anti-MAdCAM

- Anti IL-12/23
  - Ustekinumab
  - Briakinumab
  - Rizankinumab

- Jak inhibitors
  - Tofacitinib

- Anti S1 P1
  - Ozanimod

- Anti-SMAD 7
  - Mongersen
Lymphocytes Preferentially Migrate to Particular Tissues Throughout the Body

- As part of the body’s adaptive immune response, lymphocytes are imprinted for migration to areas of inflammation in certain tissues.
- Lymphocytes become imprinted in certain lymphoid tissues in which they first encounter antigen.
- After this initial activating encounter, lymphocytes preferentially leave the blood in the same type of tissue in which they became activated.
α4β7 Integrin–MAdCAM-1 is One of the Interactions That Contributes to Chronic Inflammation in UC and CD

MAdCAM-1

α4β7 integrin

Accumulation of excess infiltrating lymphocytes in the gastrointestinal tissue

Memory T lymphocyte

MAdCAM-1=mucosal addressin cell adhesion molecule-1

α4β7–MAdCAM-1 interaction has been implicated as an important contributor to the chronic inflammation that is a hallmark of UC and CD

Vedolizumab is a novel gut-selective anti-inflammatory biologic

- **Humanized mAb that binds exclusively to the α4β7 integrin heterodimer**
  - Does not bind to α4β1 or αEβ7 integrin
- **Selective antagonist of α4β7 integrin**
  - Inhibits adhesion to MAdCAM-1 and fibronectin, but not VCAM-11
- **Contains a mutated Fc region, preventing elicitation of**
  - Complement-mediated cytotoxicity
  - Antibody-dependent cellular cytotoxicity
  - Cytokine release

Fc, fragment crystallisable; mAb, monoclonal antibody; VCAM-1, vascular cell adhesion molecule

GEMINI I: vedolizumab induction therapy for UC

- **Phase 3, multicentre, prospective, RCT (N=374)**
  - Randomised 3:2, patients received VDZ 300mg (IV) or PBO on days 1 & 15
- **Mod-to-severe active UC (Mayo 8.6, mean), despite conventional therapy**
  - UC diagnosis ~6.4 yrs, CS (~54%), IS (~31%) and anti-TNF failures (~39%)
- **Rates of AEs and serious AEs were similar between VDZ and PBO groups**

**Week 6 outcomes after 2-dose induction**

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>PBO (n=149)</th>
<th>VDZ 300 mg (n=225)</th>
<th>All p&lt;0.0001 VDZ vs. PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>25 (16.6%)</td>
<td>47 (20.9%)</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>5 (3.4%)</td>
<td>17 (7.6%)</td>
<td></td>
</tr>
<tr>
<td>Mucosal healing</td>
<td>25 (16.6%)</td>
<td>41 (18.3%)</td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; CS, corticosteroid; IS, immunosuppressant; RCT, randomised controlled trial

GEMINI I: vedolizumab in UC maintenance

Primary and secondary efficacy endpoints

- Placebo (n=126)
- VDZ 300 mg every 8 weeks (n=122)
- VDZ 300 mg every 4 weeks (n=125)

**Clinical remission at 52 weeks**
- Placebo: 15.9%
- VDZ 300 mg every 8 weeks: 41.8%
- VDZ 300 mg every 4 weeks: 44.8%

**Durable clinical response (at 6 and 52 weeks)**
- Placebo: 23.8%
- VDZ 300 mg every 8 weeks: 56.6%
- VDZ 300 mg every 4 weeks: 52%

**Mucosal healing at 52 weeks**
- Placebo: 19.8%
- VDZ 300 mg every 8 weeks: 51.6%
- VDZ 300 mg every 4 weeks: 56%

GEMINI I: vedolizumab in UC maintenance

Steroid-free clinical remission

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=72</td>
<td>13.9</td>
</tr>
<tr>
<td>VDZ 300 mg q8w N=70</td>
<td>31.4</td>
</tr>
<tr>
<td>VDZ 300 mg q4w N=73</td>
<td>45.2</td>
</tr>
</tbody>
</table>

Durable clinical remission

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=126</td>
<td>8.7</td>
</tr>
<tr>
<td>VDZ 300 mg q8w N=122</td>
<td>20.5</td>
</tr>
<tr>
<td>VDZ 300 mg q4w N=125</td>
<td>24.0</td>
</tr>
</tbody>
</table>

*p<0.0001, **p=0.0079, ***p=0.0009 vs placebo.

GEMINI II: vedolizumab in CD induction

![Graph showing clinical remission and CDAI-100 response in patients with and without prior anti-TNF failure.](image)

**Induction ITT population**

- **Patients with prior anti-TNF failure** (n=175)
  - Clinical remission: 4.3%, 95% CI: -9.1, 21.3%
  - CDAI-100 response: 10.5%, 95% CI: 1.0, 13.7%

- **Patients without prior anti-TNF failure** (n=193)
  - Clinical remission: 9.0%, 95% CI: 9.3, 18.3%
  - CDAI-100 response: 28.2%, 95% CI: 10.1, 38.3%

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GEMINI II: vedolizumab in CD maintenance

Maintenance ITT population

- **Clinical remission**: Placebo 21.6%, VDZ Q8wk 39.0%, VDZ Q4wk 36.4%
- **CDAI-100 response**: Placebo 30.1%, VDZ Q8wk 43.5%, VDZ Q4wk 45.5%
- **CS-free remission**: Placebo 15.9%, VDZ Q8wk 31.7%, VDZ Q4wk 28.8%
- **Durable remission**: Placebo 21.4%, VDZ Q8wk 14.4%, VDZ Q4wk 16.2%

* *p<0.05, **p<0.01
†CS tapering began in responders at 6 weeks; for others, as soon as a clinical response was achieved.

Is there a better way forward with vedolizumab?

Bridging: co-induction with steroids?

GEMINI II: Clinical Remission at Week 6
By Concomitant Medication Use at Week 0

Patients, %

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=148)</th>
<th>VDZ (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDZ</td>
<td>7.7</td>
<td>12.1</td>
</tr>
<tr>
<td>CS only and VDZ</td>
<td>4.4</td>
<td>20.9</td>
</tr>
<tr>
<td>IMM only and VDZ</td>
<td>8.0</td>
<td>8.1</td>
</tr>
<tr>
<td>CS and IMM and VDZ</td>
<td>7.7</td>
<td>18.4</td>
</tr>
</tbody>
</table>

CS, corticosteroid; IMM, immunomodulator; VDZ, vedolizumab.
Is there a better way forward with vedolizumab?

Define timeline for response?

- Appropriate induction therapy / maintenance therapy for responders
- Role of combination therapy is being defined
- Allow 10-14 weeks for maximal induction response

GEMINI II: CDAI-100 Response Among Week 6 Non-responders*

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=69)</th>
<th>VDZ (n=351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 10</td>
<td>7.2</td>
<td>13.2</td>
</tr>
<tr>
<td>Week 14</td>
<td>11.6</td>
<td>21.7</td>
</tr>
<tr>
<td>Week 18</td>
<td>11.6</td>
<td>23.1</td>
</tr>
<tr>
<td>Week 22</td>
<td>8.7</td>
<td>23.9</td>
</tr>
<tr>
<td>Week 52</td>
<td>7.2</td>
<td>25.4</td>
</tr>
</tbody>
</table>

*In GEMINI II, 31.4% patients in the vedolizumab and 25.7% of patients in the placebo group had a CDAI-100 response at week 6. This is a post-hoc analysis; therefore P values are not reported.

Integrated Phase 2 and 3 Safety Analysis – Treatment up to 5 years

Vedolizumab and Infections: Exposure-Adjusted Incidence Rates in CD

- Data shown for patients with any infection and common infections (defined as ≥0.5 patient events/100 PY in any patient group). aGEMINI 2 and 3 studies.
bStudies C13004, GEMINI 2 and 3, and GEMINI LTS. 'MedDRA PTs listed under ‘infections and infestations’ system organ class. cMedDRA high-level terms Candida infections, fungal infections NEC, tinea infections. dMedDRA PTs listed under ‘sepsis, bacteremia, viremia and fungemia NEC’ high-level term. CD, Crohn’s disease; GI, gastrointestinal; CI, confidence interval; LTS, long-term safety; MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified; PBO, placebo; PT, preferred term; PY, person-year; VDZ, vedolizumab.

Integrated Phase 2 and 3 Safety Analysis – Treatment up to 5 years

Vedolizumab and Serious Infections: Exposure-Adjusted Incidence Rates in CD

<table>
<thead>
<tr>
<th>Event Type</th>
<th>PBO (n=355)</th>
<th>VDZ (n=1723)</th>
</tr>
</thead>
<tbody>
<tr>
<td>任何严重事件</td>
<td>3.0</td>
<td>5.6</td>
</tr>
<tr>
<td>腹泻(PT)</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>脓肿</td>
<td>0.8</td>
<td>2.4</td>
</tr>
<tr>
<td>克拉托利病</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>霉菌病,其他真菌病</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>脓肿 发热症</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>肠炎</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>病毒性淋巴细胞感染</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>革兰氏菌感染</td>
<td>0.3</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>脉管炎</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>克拉托利病,其他真菌病 NEC</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>真菌病 NEC</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

*a GEMINI 2 and 3 studies.  
b Studies C13004, GEMINI 2 and 3, and GEMINI LTS.  
c MedDRA PTs listed under ‘infections and infestations’ system organ class.  
d MedDRA PTs anal abscess, perirectal abscess, rectal abscess, rectovaginal septum abscess, abdominal abscess, abscess intestinal, abscess perineal abscess, pelvic abscess.  
e MedDRA high-level terms Candida infections, fungal infections NEC, tinea infections.  
f MedDRA PTs under ‘sepsis, bacteremia, viremia and fungemia NEC’ high-level term.  
CD, Crohn’s disease; CI, confidence interval; LTS, long-term safety; MedDRA, Medical Dictionary of Regulatory Activities; NEC, not elsewhere classified; PBO, placebo; PT, preferred term, PY, person-year; VDZ, vedolizumab.

Etrolizumab

- Etrolizumab is a humanized mAB that targets the integrin receptors that regulate trafficking and retention of leukocyte/lymphocyte subsets in the intestinal mucosa signals.
- Etrolizumab differs from vedolizumab by blocking $\alpha E\beta 7$ as well as $\alpha 4\beta 7$.
- Etrolizumab is GI specific and targets $\beta 7$ not $\alpha 4\beta 1$, therefore risk PML thought to be low.
Phase II: safety and efficacy of etrolizumab (humanized anti-beta7 mAb) for moderate-to-severe UC

- Phase 2, multicentre, prospective, RCT (N=119)
  - Randomised 1:1:1, patients received ETZ 100 mg/mo s.c. or 420 mg loading dose between Week 0 & 2 then 300 mg/mo s.c. or PBO for 3 doses
- Moderate-to-severe active UC: Mayo ≥5, endoscopy subscore ≥ 2 and RBS ≥1
- UC diagnosis ~9 yrs, mean Mayo ~9, CS (~42%), IS (~38%), anti-TNF failures (~60%)
- Rates of AEs were comparable between ETZ and PBO groups

ETZ, etrolizumab; RBS, rectal bleed severity.
Clinical remission: Mayo score ≤ 2 with no individual score >1. Endoscopic remission: Mayo endoscopy subscore 0.

Phase II: PF-00547659 (Anti-MAdCAM-1 mAb) for Mod-Sev UC

- Phase IIa: N = 357 mod-sev UC pts (total Mayo ≥ 6; endo subscore ≥ 2) were randomized to PBO, 7.5 mg, 22.5 mg, 75 mg or 225 mg PF-00547659, q4w (s.c.)
- BL mean Mayo (~8.4); anti-TNF failures (~43%)
- PF-00547659 appears to be well-tolerated and not associated with increased rate of infection

**Primary and Secondary Endpoints at Week 12**

- **Clinical Remission**
  - PBO (n = 83)
  - PF 7.5 mg (n = 71)
  - PF 22.5 mg (n = 70)
  - PF 75 mg (n = 73)
  - PF 225 mg (n = 70)

- **Clinical Response**
  - Primary Endpoint
  - *P < 0.05 vs. PBO

- **Mucosal Healing**
  - PBO (n = 83)
  - PF 7.5 mg (n = 71)
  - PF 22.5 mg (n = 70)
  - PF 75 mg (n = 73)
  - PF 225 mg (n = 70)

*P < 0.05 vs. PBO
Phase II: PF-00547659 (Anti-MAdCAM-1 mAb) for Active Refractory, TNF-Experienced CD

**Number in each group:**
- PBO (n = 63)
- PF 22.5 mg (n = 67)
- PF 75 mg (n = 64)
- PF 225 mg (n = 68)

**Primary Endpoint (CDAI-70):**
- PBO: 59%
- PF 22.5 mg: 62%
- PF 75 mg: 65%
- PF 225 mg: 58%

**Remission (BL CRP > 18):**
- PBO: 23%
- PF 22.5 mg: 27%
- PF 75 mg: 28%
- PF 225 mg: 29%

**Remission (BL CRP > 18) rates similar:**
- All P = NS

**Summary Points:**
- **Phase IIa:** N = 267 CD pts (CDAI 220-450) randomized to PBO, 22.5 mg, 75 mg or 225 mg PF-00547659, q4w (s.c.)
- **BL disease duration (~11 yrs); mean CDAI (~315):** All pts were anti-TNF experienced with elevated hsCRP (> 3.0 mg/L)
- **Rates of AEs similar,** higher numerical GI infections noted in PF vs. PBO
S1P Receptor Modulators and the S1P Signalling Pathway

- S1P receptor modulators prevent migration of lymphocytes from lymph nodes to sites of inflammation where they contribute to immune-mediated pathology.

S1P receptor modulation

Lymph node (low S1P concentration)

Endothelium

Lymph (high S1P concentration)

Lymphocyte egression blocked

Signalling

Lymphocyte

S1P modulators

S1P

Internalised S1P

Degraded S1P

Phase II Trial of Ozanimod (S1P1 Receptor Modulator) in Mod-Sev UC

Clinical Remission: Mayo Score ≤ 2, no subscore >1; Clinical Response: reduction ≥ 3 points and ≥ 30% of the Mayo score with a decrease in RBS of ≥1 or RBS ≤1

<table>
<thead>
<tr>
<th></th>
<th>Week 8</th>
<th>Week 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose (N=65)</td>
<td>13.8%</td>
<td>26.2%</td>
</tr>
<tr>
<td>High dose (N=67)</td>
<td>58.2%</td>
<td>53.8%</td>
</tr>
<tr>
<td>Placebo (N=65)</td>
<td>16.4%</td>
<td>6.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Week 8</th>
<th>Week 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose (N=65)</td>
<td>34.3%</td>
<td>27.7%</td>
</tr>
<tr>
<td>High dose (N=67)</td>
<td>50.7%</td>
<td>36.9%</td>
</tr>
<tr>
<td>Placebo (N=65)</td>
<td>12.3%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*P<0.05 vs placebo; **P<0.01 vs placebo
Biology and site of action of interleukins 12 and 23

- Ustekinumab and risankizumab are fully human monoclonal IgG1 antibodies
- Ustekinumab bind the p40 subunit of IL-12/23
- Risankizumab is a selective blocker of the IL23 p19 subunit
- Ustekinumab is approved for the treatment of PsA and plaque psoriasis
Ustekinumab for induction Therapy in CD: Results of Phase 3 UNITI 1 and UNITI 2: Clinical Remission (CDAI<150)

Ustekinumab Reduces CRP at Weeks 3, 6 and 8

Mean CRP Concentration Change by Week 8

Mean Change from Baseline CRP (mg/L)

-10 -8 -6 -4 -2 0 2 4

Weeks

0 1 2 3 4 5 6 7 8

all p<0.001 vs. PBO

-0.18 1.03 -0.14

-4.76 -5.97 -3.97

-8.61 -8.41 -8.56

PBO
UST 130 mg
UST ~6 mg/kg

Subjects who had insufficient data at the designated analysis time point had their last value carried forward.

Ustekinumab for Maintenance in CD: Results of Phase III

Phase IIa: Induction Study of MEDI2070 (Anti-p19 mAb) for Active, anti-TNF-refractory CD

- Phase II: N = 121 mod-sev CD pts (CDAI 220-450), Randomized to PBO or MEDI2070 700 mg IV at weeks 0 and 4
- BL CDAI ≈320; dis. duration (~12 yrs); prior surg. (~45%); 31/58/11% failed 1/2/3 anti-TNF’s
- MEDI2070, demonstrated clinical effect and favorable safety profile over 12wks

**Efficacy Outcomes at Week 8**

- **Clinical Effect:** CDAI-100 response or CDAI <150)
- **Clinical Remission:** CDAI <150
- **Clinical Response:** CDAI <150 or CRP/FC reduction ≥50%
- **Clinical + Biomarkers:** Clinical Effect & ≥50% reduction in BL CRP or FC

**Primary Endpoint**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PBO (n = 60)</th>
<th>MEDI2070 (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Effect</td>
<td>27%</td>
<td>49%</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>15%</td>
<td>27%</td>
</tr>
<tr>
<td>Clinical Response</td>
<td>25%</td>
<td>46%</td>
</tr>
<tr>
<td>Clinical + Biomarkers*</td>
<td>10%</td>
<td>42%</td>
</tr>
</tbody>
</table>

*P = 0.010

Sands et al. ECCO 2015, Abstract OP025
Efficacy and Safety of Risankizumab as Induction Therapy in CD


**Summary of Key Clinical Outcomes at Week 12**

- **Primary Endpoint**
  - Clinical Remission: CDAI of <150 points from BL
  - Clinical Response: CDAI of <150 points or a CDAI reduction from BL of ≥100 points
  - Endoscopic Remission: CDEIS of ≤4
  - Endoscopic Response: defines as a >50% CDEIS reduction from BL

- **Phase IIb, multicentre, RCT of risankizumab (humanized anti-IL-23p19 mAb)**
  - N=121 randomized to receive i.v. q4w of RSK 200 mg, 600 mg or PBO
  - Mod-to-sev CD (mean CDAI ~298), CD dx (~13 yrs), aTNF-experienced (94%)
  - AE rates were similar between RSK and PBO & no dose-related associations

<table>
<thead>
<tr>
<th>Remission</th>
<th>Response</th>
<th>Endoscopic Remission</th>
<th>Endoscopic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO (n = 39)</td>
<td>RSK 200 mg (n = 41)</td>
<td>RSK 600 mg (n = 41)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>21</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>24</td>
<td>37</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>37*</td>
<td>42*</td>
<td>20*</td>
<td>37*</td>
</tr>
</tbody>
</table>

* p < 0.05
Phase 2 Psoriasis: Risankizumab vs. ustekinumab \textit{PASI Results}

*18 mg BI 655066 only given once at Week 0. Analysis includes all patients who were randomized and who received at least one dose of assigned therapy during the study with nonresponder imputation.

Papp K, et al. EADV 2015, FC03.06 Sponsored by Boehringer Ingelheim
The anti-IL-23 and anti-IL-17 wars in psoriasis

?Best-in-class Biologic?

- Dosing has potential to be the most patient friendly at once every 3 months
- Potential for durability above IL-12/23 and IL-17s at one year

Comparison of PASI90 Scores at 12 wks

Comparison of PASI100 Scores at 12 wks

Sources: Humira (CHAMPION and REVEAL), Stelera (PHEONIX 1 and 2), COSENTYX (ERASURE and FIXTURE), Ixekizumab (UNCOVER 1, 2, 3), Tildrakizumab (Merck AAD 2013), Guselkumab (NEJM 2015), BI655066 (EADV 2015)
Tofacitinib (CP-690,550) blocks phosphorylation of STAT and downstream activation

- Tofacitinib (CP-690,550) is a novel, small-molecule, oral JAK inhibitor that is being investigated as a targeted immunomodulator for several inflammatory diseases including ulcerative colitis.
- Tofacitinib inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular specificity for JAK1 and JAK3 over JAK2. Importantly, tofacitinib directly or indirectly modulates signaling for an important subset of pro-inflammatory cytokines including IL-2, -4, -7, -9, -15, and -21.

**Cytokine Effects on the immune system**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Effects on the immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>Stimulate the proliferation and differentiation of Th, Tc, B, and NK cells</td>
</tr>
<tr>
<td>IL-4</td>
<td>Induce the differentiation of Th0 to Th2, Induce Ig switching</td>
</tr>
<tr>
<td>IL-7</td>
<td>Promote the development, proliferation and survival of T, B, and NK cells</td>
</tr>
<tr>
<td>IL-9</td>
<td>Stimulate intrathymic T cell development</td>
</tr>
<tr>
<td>IL-15</td>
<td>Promote the proliferation, cytotoxicity and cytokine production of NK cells</td>
</tr>
<tr>
<td>IL-21</td>
<td>Enhance T and B cell function</td>
</tr>
</tbody>
</table>

Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; NK, natural killer; STAT, signal transducer and activator of transcription; Th, T helper; Tc, cytotoxic T cell

Safety data showed no new or unexpected observations from results in tofacitinib studies in other populations.

**P<0.01 vs placebo; ***P<0.001 vs placebo. BID=twice daily; TNFi=tumor necrosis factor inhibitor.

Rapid and significant improvements in partial Mayo score were observed as early as Week 2.

***P<0.001 vs placebo (linear mixed-effects model). BID=twice daily.
BID=twice daily; SE=standard error.
Pfizer press release

July 28, 2016

“Pfizer Inc. announced today top-line results from Oral Clinical Trials for tofacitinib in ulcerative colitis (OCTAVE) Sustain, the third Phase 3 study of tofacitinib citrate being investigated in patients with moderately to severely active ulcerative colitis (UC).

Top-line results from the OCTAVE Sustain study showed that the proportion of patients in remission at Week 52, the primary efficacy endpoint, was significantly greater in both the tofacitinib 5 and 10 mg BID groups compared to placebo. No new or unexpected safety findings for tofacitinib were observed in the study.”

BID=twice daily.
Inhibition of IL-6

- IL-6's role as an anti-inflammatory cytokine is mediated through its inhibitory effects on TNF-alpha and IL-1, and activation of IL-1ra and IL-10.
- PF-04236921 is a fully human antibody that binds to and neutralizes the IL-6 ligand.
Anti-IL-6 Antibody (PF-04236921) in Subjects with CD Who Are Anti-TNF Inadequate Responders: Week 12

n=249

2 doses sc @ week 0 and 4
Anti-IL-6 Antibody (PF-04236921) in Subjects with Crohn’s Disease

Danese, Panaccione et al. Submitted NEJM
Anti-IL-6 Antibody (PF-04236921) in Subjects with Crohn’s Disease: Suppression of CRP
SMAD7 Inhibition and the TGF-β/SMAD Pathway

- Inhibition of SMAD7 restores SMAD2/3 activity and TGF-β-mediated signaling, thereby suppressing the production of proinflammatory cytokines\(^1\)

- Mongersen Phase 2 study in UC is ongoing\(^2\)

2. ClinicalTrials.gov NCT02601300.
Smad7 Antisense Oligonucleotide Proposed Mechanism of Action

- In IBD, Smad7 appears over-expressed and this may result in decreased activity of TGF-β1 which is protective against an inflammatory state.

- GED-0301 (Mongersen) is an oral antisense DNA oligonucleotide targeting Smad7 mRNA.

- In mouse models, knockout of Smad7 restores TGF-β1 activity, with the downstream effect of inhibiting inflammatory cytokine production.

Monteleone et al. (2012) Mol Ther 20: 870-876
Phase IIa: Mongersen (GED-0301) in Active Crohn’s Disease

- Phase IIa: N = 126 CD pts dosed for 14 days, with 3 mo f/u
- CS-dependent/resistant mod-sev CD with ileal involvement (CDAI 220-400); no strictures/fistulae; CD dx ~10 yrs, median CDAI ~250, Con-IS (~32%)
- Primary endpoint: Remission* achieved in 55% (40 mg/d) and 65% (160 mg/d) vs 9.5% PBO; P < 0.0001 (no significant difference for 10 mg/d; 12.2%)
- Rates of AEs and SAEs were similar across groups
  *Clinical Remission (CDAI < 150 at day 15 and maintained for ≥ 2 wks)

CDAI Remission Over 3 Months

- *P < 0.0001 vs. PBO
- #P ≤ 0.0008 vs. PBO

<table>
<thead>
<tr>
<th>Fraction of Pts (%)</th>
<th>Day 15</th>
<th>Day 28</th>
<th>Day 84</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>21/42</td>
<td>14/42</td>
<td>21/42</td>
</tr>
<tr>
<td>MNG 10 mg/d</td>
<td>58/40</td>
<td>29/40</td>
<td>29/43</td>
</tr>
<tr>
<td>MNG 40 mg/d</td>
<td>58/40</td>
<td>29/40</td>
<td>29/43</td>
</tr>
<tr>
<td>MNG 160 mg/d</td>
<td>67/43</td>
<td>72/43</td>
<td>63/40</td>
</tr>
</tbody>
</table>
Phase IIb: Mongersen Endoscopic and Clinical Outcomes Study
ΔCDAI Mean Change From Baseline Through Week 12

Data From All Treatment Groups

Mean Change From Baseline in CDAI Score†

Study Week

-160 -140 -120 -100 -80 -60 -40 -20 0

n= 63 56 62 44 21

*P<0.0001

* CDAI mean change from baseline at Week 12 was determined in the ITT population using LOCF methodology.

Pooled analysis of 3 dosing groups
GED 301 160mg X 4 weeks
GED 301 160 mg X 8 weeks
GED 301 160 mg X12 weeks

Phase IIb: Mongersen Endoscopic and Clinical Outcomes Study

Clinical response week 12

Clinical remission week 12

Patients Achieving Clinical Response* (%) | Patients Achieving Clinical Remission* (%)

GED-0301 Treatment Group

<table>
<thead>
<tr>
<th>4 Weeks (N=19)</th>
<th>8 Weeks (N=23)</th>
<th>12 Weeks (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td>44</td>
<td>67</td>
</tr>
</tbody>
</table>

GED-0301 Treatment Group

<table>
<thead>
<tr>
<th>4 Weeks (N=19)</th>
<th>8 Weeks (N=23)</th>
<th>12 Weeks (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>35</td>
<td>48</td>
</tr>
</tbody>
</table>

Phase IIb: Mongersen Endoscopic Response at Week 12: SES-CD Reduction by ≥25% and ≥50%

SES-CD Reduction by ≥25%

Patients Achieving Endoscopic Response* (%)

- All Evaluable Patients: 19/52 (37%)
- Baseline SES-CD >12: 10/16 (63%)

SES-CD Reduction by ≥50%

Patients Achieving Endoscopic Response* (%)

- All Evaluable Patients: 8/52 (15%)
- Baseline SES-CD >12: 5/16 (31%)

*Data as observed.
Summary

- Emerging strategies are defining improved ways of managing patients with IBD

- New therapies provide us with more choice and greater treatment flexibility

- Our task is to use the right treatment in the right patient at the right time
  - Explore the evidence base
  - Understand best practice
  - Optimise your first biologic
  - Tailor treatment to patient needs