Inflammatory bowel disease: Novel therapies
NZ November 2018

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Consultant Gastroenterologist
From the Edinburgh IBD Unit at the Western General Hospital
History of treatment for IBD

- 1950s: First use of steroids
- 1960: First use of thiopurines
- 1989: First MTX study in CD
- 1990s: First approval of anti-TNFs
- 2015: Start of the biosimilar era
- 2014: Vedolizumab launched; first gut-selective agent for IBD
- 2017: Ustekinumab launched for CD
- 2018–2019: Tofacitinib approved for UC/JAK inhibitors
Current therapies for IBD (September 2018)

**Induction agents**
- Corticosteroids
- 5-ASA (UC only)
- Anti-TNF agents
- Vedolizumab
- Ustekinumab (Crohn’s only)
- Exclusive enteral feeding (ileal Crohn’s)
- Limited surgical resection

**Maintenance agents**
- 5-ASA (UC only)
- Azathioprine / MP
- Methotrexate (Crohn’s)
- Anti-TNF agents
- Vedolizumab
- Ustekinumab (Crohn’s only)
- Smoking cessation
## Benefits of biologic agents

Clinical trials in Crohn’s disease have shown:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Adalimumab</th>
<th>Infliximab*</th>
<th>Vedolizumab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction of remission</td>
<td>CLASSIC-1</td>
<td>Targan et al. 7</td>
<td>GEMINI II 9</td>
<td>UNITI-1 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GEMINI III 10</td>
<td>UNITI-2 12</td>
</tr>
<tr>
<td>Fast onset of action</td>
<td>CLASSIC-1</td>
<td>Targan et al. 7</td>
<td>GEMINI II 9</td>
<td>UNITI-1 12</td>
</tr>
<tr>
<td></td>
<td>GAIN 2</td>
<td></td>
<td></td>
<td>UNITI-2 12</td>
</tr>
<tr>
<td>Long-term remission</td>
<td>ADHERE (3yr) 3</td>
<td>ACCENT-1 (1yr) 8</td>
<td>GEMINI II (1 yr) 9</td>
<td>IM-UNITI (44 wks) 12</td>
</tr>
<tr>
<td>Mucosal healing</td>
<td>EXTEND 4</td>
<td>ACCENT-1 8</td>
<td>VERSIFY</td>
<td>GETAID 13</td>
</tr>
<tr>
<td>Reduced hospital admissions and operations</td>
<td>CHARM / ADHERE 5 EXTEND 6</td>
<td>ACCENT-1 8</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Remicade® (MSD)

### Do Conventional and Anti-TNFα Therapies Meet the Goals of Crohn’s Disease Treatment?

<table>
<thead>
<tr>
<th>Goal</th>
<th>5-ASA</th>
<th>Steroids</th>
<th>AZA</th>
<th>MTX</th>
<th>Anti-TNFα</th>
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</thead>
<tbody>
<tr>
<td><strong>Short-term endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical remission</td>
<td>✗</td>
<td>✓ 1</td>
<td>✓ 1</td>
<td>✓ 2</td>
<td>✓ 3</td>
</tr>
<tr>
<td>Steroid-free clinical remission</td>
<td>✗</td>
<td>✗</td>
<td>✓ 1</td>
<td>✓ 2</td>
<td>✓ 4</td>
</tr>
<tr>
<td>Clinical and mucosal remission</td>
<td>✗</td>
<td>✗</td>
<td>✓ 5</td>
<td>?</td>
<td>✓ 3,4</td>
</tr>
<tr>
<td><strong>Long-term disease modification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction of surgical risk</td>
<td>?</td>
<td>?</td>
<td>Conflicting data&lt;sup&gt;6&lt;/sup&gt;</td>
<td>?</td>
<td>✓ 7</td>
</tr>
<tr>
<td>Reduction of “damage”</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

No prospective head-to-head trials exist. No comparative conclusions should be made. 5-ASA=5-aminosalicylic acid; AZA=azathioprine; MTX=methotrexate; TNFα=tumor necrosis factor alpha.

Crohn’s: Predictors of Serious Infection

TREAT Registry: Predictors of Serious Infection

- Moderate-to-severe disease activity: Hazard Ratio (95% CI) = 2.24, \( P < 0.001 \)
- Narcotic analgesic treatment: Hazard Ratio (95% CI) = 1.98, \( P < 0.001 \)
- Prednisone therapy: Hazard Ratio (95% CI) = 1.57, \( P = 0.002 \)
- Infliximab treatment: Hazard Ratio (95% CI) = 1.43, \( P = 0.006 \)

Crohn’s disease: TREAT registry, >5 years of follow-up (N=5394)
Anti-TNFα Therapies Are Associated with Gradual Loss of Response Over Time


TNFα=tumor necrosis factor alpha.
Evolution of treatment goals

Clinical remission
Evolution of treatment goals

**Clinical remission**
- 1970
- 1980
- 1990
- 2000
- 2010
- 2020

**Steroid-free remission**

**Biochemical and endoscopic remission**
- 1970
- 1980
- 1990
- 2000
- 2010
- 2020

- Increasing use of calprotectin
Evolution of treatment goals

- Clinical remission
- Steroid free remission
- Deep remission
- Biochemical and endoscopic remission
- Increasing use of calprotectin
- Treat-to-target

1970 to 2020 timeline:
- Clinical remission
- Steroid free remission
- Deep remission
- Biochemical and endoscopic remission
- Increasing use of calprotectin
- Treat-to-target
Treating a patient with Crohn’s disease

Resolution of abdominal pain and normalisation of bowel habit should be the target

Assess outcomes at least every 3 months until resolution

After symptom resolution, outcomes should be assessed at least every 6–12 months

AND

Treating intestinal inflammation

Absence of ulceration is the target

Endoscopy or cross-sectional imaging should be performed within 6–9 months after treatment starts

Histological remission and biomarkers (CRP/FC) are not targets

Failure of CRP or FC normalisation should prompt further endoscopic evaluation, irrespective of symptoms
Induction therapy & tight monitoring

Mild disease
- Budesonide/corticosteroids

Moderate disease
- EEN or CS + AZA
- - risk factors
- + risk factors

Severe disease
- Anti-TNF + AZA

+ Tight monitoring

AZA: Azathioprine; CS: corticosteroid therapy; EEN: exclusive enteral nutrition
Dr Charlie Lees, personal algorithm
UK/EYV/1803/0027k
April 2018
**Induction therapy & tight monitoring**

- **Mild disease**: Budesonide/corticosteroids
- **Moderate disease**
  - - risk factors: Anti-TNF monotherapy
  - + risk factors: Anti-TNF + AZA
- **Severe disease**: Anti-TNF + AZA

Tight monitoring is advised throughout to monitor for any adverse effects or disease progression.

Poor predictive ability means we are very reliant on tight monitoring.
Young age

Smoking

Extensive small bowel disease

Peri-anal disease

Steroids at diagnosis
(Beaugerie L, et al. Gastroenterology. 2006;130:650-6)

Weight loss

Deep ulcerations at endoscopy
Layer in big data from multiple omics sources
- clinical and molecular phenotyping
- machine learning and AI
- hyper-personalized care

Young age

Smoking

Extensive small bowel disease

Peri-anal disease

Steroids at diagnosis
(Beaugerie L, et al. Gastroenterology. 2006;130:650-6)

Weight loss

Deep ulcerations at endoscopy
Induction therapy & tight monitoring

Mild disease

Moderate disease
- risk factors
+ risk factors

Severe disease

Induction therapy & tight monitoring

>???>

Anti-TNF monotherapy
vedolizumab
Anti-TNF + AZA

JAK inhibitors
ustekinumab
Treating to target is established in other chronic inflammatory diseases

Rheumatoid arthritis\(^1,2\)

Remission / low disease activity

Psoriasis\(^3-5\)

BSA, PASI, DLQI
PGA score

Psoriatic arthritis\(^6,7\)

Remission / low disease activity

BSA, body surface area; PASI, psoriasis area severity index; PGA, physician global assessment; DLQI, dermatology life quality index

TICORA demonstrated the value of tight control in rheumatoid arthritis

**Rheumatoid arthritis**

Remission / low disease activity

Patients with active RA randomised to intensive management or routine care for 18 months

<table>
<thead>
<tr>
<th>Intensive management (n=55)</th>
<th>Visit every month: Disease activity score calculated; If score &gt;2.4, therapy escalated as per protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine care (n=55)</td>
<td>\n</td>
</tr>
</tbody>
</table>

Compared with routine care, intensive management:
- Reduced disease activity
- Reduced radiographic disease progression
- Improved physical function and quality of life
- Incurred no additional costs

Use of biologics and reduced surgical rates in Crohn’s disease

Surgical trends in CD population-based studies

Year

5-year surgery rate
0 20 40 60 80 100

PRE-BIOLOGIC ERA
BIOLOGIC ERA

IBSEN
Stockholm County
Cardiff
Olmstead County
Copenhagen County
Manitoba
Danish National Patient Register

Size of circle represents number of patients in cohort

Can treating to target further decrease the number of surgeries?

Treating to target in IBD: proposed stepwise algorithm for clinical practice

1. Assess risk factors
2. Set appropriate target
3. Treat in a timely manner
4. Monitor regularly
5. Optimise therapy as necessary

TARGET ACHIEVED

TARGET NOT ACHIEVED

Target recommendations for Crohn’s disease: treat beyond symptoms*

Resolution of abdominal pain and normalisation of bowel habit
• Assess at least every 3 months during active disease

Resolution of ulceration
• Assess 6–9 months during the active phase

Biomarkers: CRP and FCP are adjunctive measures of inflammation for monitoring CD (not targets)

Failure of CRP or FCP normalisation should prompt further endoscopic evaluation, irrespective of symptoms

*Resolution of symptoms alone is not a sufficient target; objective evidence of inflammation of the bowel is necessary when making clinical decisions

STRIDE, Selecting Therapeutic Targets in IBD; CRP, C-reactive protein; FCP: faecal calprotectin; PRO, patient-reported outcome

Timely referral and diagnosis, followed by implementing a treat-to-target approach, could potentially improve outcomes for patients with IBD.

1. Life before illness
2. Onset of symptoms
3. Timely referral
4. Timely diagnosis
5. Assess risk factors
6. Set appropriate target
7. Treat in a timely manner
8. Diagnosis and management plan
9. Monitor regularly
10. Optimise therapy
11. Achieve target

Dr Charlie Lees PhD FRCP(Ed)
@charlie_lees  charlielees.com
Timely referral and diagnosis, followed by implementing a treat-to-target approach, could potentially improve outcomes for patients with IBD.
Starting anti-TNF therapy: the importance of timing

<table>
<thead>
<tr>
<th>Trial</th>
<th>Timepoint</th>
<th>Remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUTD1</td>
<td>≤2 years</td>
<td>≥80</td>
</tr>
<tr>
<td>SONIC2</td>
<td>≤2 years</td>
<td>≥70</td>
</tr>
<tr>
<td>DIAMOND3</td>
<td>&gt;2 years</td>
<td>≥50</td>
</tr>
<tr>
<td>GETAID3</td>
<td>≥2 years</td>
<td>≥40</td>
</tr>
<tr>
<td>PRECISE 2*</td>
<td>&lt;1 year</td>
<td>≥30</td>
</tr>
<tr>
<td>PRECISE 2*</td>
<td>≥5 years</td>
<td>≥20</td>
</tr>
<tr>
<td>ACCENT 1*</td>
<td>≥5 years</td>
<td>≥10</td>
</tr>
<tr>
<td>CHARMS</td>
<td>≤2 years</td>
<td>≥10</td>
</tr>
<tr>
<td>CHARMS</td>
<td>&gt;2 years</td>
<td>&lt;10</td>
</tr>
<tr>
<td>DIAMOND5</td>
<td>&gt;2 years</td>
<td>&lt;10</td>
</tr>
<tr>
<td>DIAMOND9</td>
<td>&gt;2 years</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

The products used in the clinical trials listed here may differ with respect to indications, safety, and efficacy, and are not bioequivalent. Patient baseline characteristics and concomitant therapies in trials can differ. No conclusions regarding comparative safety or efficacy can be drawn from this information.

*Remission evaluated after 26 weeks of treatment.

Treating to target is a disease-management strategy intended to improve patient outcomes

- Treating to target goes beyond symptom resolution to also reduce inflammation and improve patient quality of life
- Control of inflammation may help halt disease progression and prevent bowel damage and disability

Treating to target involves:
1. Assessing risk factors
2. Setting an appropriate target
3. Treating in a timely manner
4. Monitoring regularly
5. Optimising therapy as necessary
CALM: Evidence for a treat-to-target approach in IBD

• Open-label, multicentre study in patients with early* moderate-to-severe CD
• Patients (n=244) randomised to:
  - **Tight control** (treat-to-target approach) – Treatment optimisation based on biomarkers (CRP, FCP), steroid use and clinical symptoms (CDAI)
  - **Clinical management** – Treatment optimisation based on steroid use and clinical symptoms (CDAI)
• **Monitored** every 12 weeks
• Primary endpoint was mucosal healing (CDEIS <4) with absence of deep ulcers at week 48

CALM is the **first study** to show that **timely optimisation of therapy based on clinical symptoms combined with biomarkers** in patients with early* CD results in **improved clinical and endoscopic outcomes** than optimisation based on symptoms alone

*Early CD defined in CALM as CD diagnosis confirmed by endoscopy not >6 years before baseline
CDEIS, Crohn’s Disease Endoscopic Index of Severity; CRP, C-reactive protein; FCP, faecal calprotectin
CALM primary outcomes:

Superior endoscopic and deep remission outcomes with treat-to-target

- **Primary endpoint**
  - CDEIS <4 and absence of deep ulcer
    - Treat-to-target group (n=122): 45.9%
    - Clinical management (n=122): 30.3%
    - p=0.010

- **Deep remission**
  - CDAI <150; no steroids for 8 weeks; no draining fistula; CDEIS <4; no deep ulcers
    - Treat-to-target group (n=122): 36.9%
    - Clinical management (n=122): 23.0%
    - p=0.014

- **Biologic remission**
  - Calprotectin <250 µg/g; CRP <5 mg/L; CDEIS <4
    - Treat-to-target group (n=122): 29.5%
    - Clinical management (n=122): 15.6%
    - p=0.006


CDAI, Crohn’s Disease Activity Index; CDEIS, Crohn’s Disease Endoscopic Index of Severity.
New mechanisms of action and future therapies for IBD?
CALM revisited ...

Superior endoscopic and deep remission outcomes with treat-to-target

- CDEIS <4 and absence of deep ulcer
  - Treat-to-target group (n=122): 30.3%
  - Clinical management (n=122): 56%
  - p = 0.010

- Deep remission
  - CDAI <150; no steroids for 8 weeks; no draining fistula; CDEIS <4; no deep ulcers
  - Treat-to-target group (n=122): 23.0%
  - Clinical management (n=122): 45%
  - p = 0.014

- Biologic remission
  - Calprotectin <250 µg/g; CRP <5 mg/L; CDEIS <4
  - Treat-to-target group (n=122): 15.6%
  - Clinical management (n=122): 36%
  - p = 0.006

Vedolizumab is the only gut-selective integrin inhibitor with marketing authorization for moderate to severe UC or CD.
Scottish Vedolizumab Cohort

Plevris N and Lees CW (2018; submitted)
Scottish Vedolizumab Cohort: CD

Figure 2. Kaplan-Meier curves for Crohn’s disease treatment outcomes stratified by previous TNFα exposure. A, cumulative rates of clinical remission; B, cumulative rates of mucosal healing; C, cumulative rates of deep remission; D, cumulative rates of colectomy.

Plevris N and Lees CW (2018; submitted)
Scottish Vedolizumab Cohort: UC

Figure 2. Kaplan-Meier curves for ulcerative colitis treatment outcomes stratified by previous TNFα exposure. A, cumulative rates of clinical remission; B, cumulative rates of mucosal healing; C, cumulative rates of deep remission; D, cumulative rates of colectomy.
Patients in clinical remission from Week 44 through Week 92 of IM-UNITI LTE: Observed data*

Remission rates among randomised patients who entered the LTE

*Evaluates rates of remission observed during the first year of the LTE (Weeks 44–92) in IV UST induction responders randomised in IM-UNITI who entered the LTE and remained on treatment at that specific time point.

IV: intravenous; LTE: long-term extension; q8/12w: every 8/12 weeks; SC: subcutaneous; UST: ustekinumab

*products not licensed for use in IBD in the UK


UK/EVV/1803/0027k
April 2018
Risankizumab* Phase II psoriasis

Grey arrow: risankizumab 18mg single dosing; black arrows: risankizumab (90mg or 180mg) and ustekinumab multiple dosing


*Risankizumab not licensed for use in IBD in the UK
Risankizumab* Phase II Crohn’s disease
Patients in clinical remission (CDAI <150) at week 12 – primary endpoint

Adjusted ∆ and p-values are for comparisons vs. placebo.

Full analysis set was used for this analysis, using non-response imputation for missing values and stratified Cochran-Mantel-Haenszel test.

CDAI: Crohn’s disease activity index.

*Risankizumab not licensed for use in IBD in the UK

UK/EYV/1803/0027k
April 2018
Risankizumab* Phase II Crohn’s disease
Patients with endoscopic remission at week 12

Endoscopic remission is a CDEIS score of ≤4 at Week 12 for patients with initial isolated ileitis a score of ≤2.

Full analysis set was used for this analysis, using non-response imputation for missing values and stratified Cochran-Mantel-Haenszel tests. Adjusted Δ and p-values are for comparisons vs. placebo. CDEIS, Crohn’s Disease Endoscopic Index of Severity.


*Risankizumab not licensed for use in IBD in the UK
*products not licensed for use in IBD in the UK

JAK inhibitors

What are they?

- Intracellular small molecules that inhibit the JAK/STAT signalling pathway\(^1,2\)

Why they may work in IBD

- JAKs play an essential role in inflammatory signalling\(^1\)
- JAK/STAT pathway is implicated in the pathogenesis of immune-mediated inflammatory conditions, including IBD\(^1\)

What are the potential candidates?

- Tofacitinib* (CD: discontinued; UC: Phase III)\(^2\)
- Filgotinib* (CD: Phase III; UC: Phase III)\(^2\)
- Upadacitinib* (CD: Phase II; UC: Phase II)\(^1\)
- Peficitinib* (UC: Phase II)\(^1\)

Distinct profiles of JAK inhibitors

\(\text{JAK1} > \text{JAK2} > \text{TYK2}\)

- Tofacitinib\(^3\)
- Filgotinib\(^5\)
- Upadacitinib\(^6\)
- Peficitinib\(^4\)

\*products not licensed for use in IBD in the UK

References:

Tofacitinib UC Phase 3 Program

OCTAVE Induction 1
A3921094

- 10 mg BID
- Placebo
- 8 weeks* N=598 (4:1)

Nonresponders

OCTAVE Induction 2
A3921095

- 10 mg BID
- Placebo
- 8 weeks* N=541 (4:1)

Nonresponders

OCTAVE Sustain
A3921096

- 10 mg BID
- 5 mg BID
- Placebo

Responders

OCTAVE Sustain
A3921096

- 52 weeks* N=593 (1:1:1)

Completers & Treatment Failures

OCTAVE Open
A3921139

- 5 mg BID†
- 10 mg BID†

Assessment

Enrollment

Up to 1st approval N=944

*Final complete efficacy assessment at Week 8/52. Treatment continued up to Week 9/53. † Subjects in remission at OLE baseline: 5 mg BID; all others: 10 mg BID.

BID=twice daily; OLE=open-label extension.


5. Pfizer data on file.
Tofacitinib: Induction and maintenance results from three Phase III trials in UC

**Week 8 results**

**OCTAVE Induction 1**
Inadequate response to IMM, CS or TNFs
- Tofacitinib 10 mg BID (n=476)
- Placebo (n=122)
- P=0.007

**OCTAVE Induction 2**
Inadequate response to IMM, CS or TNFs
- Tofacitinib 10 mg BID (n=429)
- Placebo (n=112)
- P<0.001

**Week 52 results**

**OCTAVE Sustain**
OCTAVE 1 and 2 completers
- Tofacitinib 10 mg BID (n=197)
- Tofacitinib 5 mg BID (n=198)
- Placebo (n=198)
- P<0.001

- Remission†
  - Tofacitinib: 40.6, Placebo: 11.1
  - P<0.001

- Mucosal healing‡
  - Tofacitinib: 45.7, Placebo: 13.1
  - P<0.001

†Mayo score ≤2 with no subscore >1 and a rectal bleeding score of 0; ‡Mayo endoscopic subscore ≤1.

Primary Endpoint: Remission at Week 8 By Prior TNFi Treatment

**OCTAVE Induction 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Tofacitinib 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFi-treated</td>
<td>1.5</td>
<td>12.6</td>
</tr>
<tr>
<td>TNFi-naive</td>
<td>15.8</td>
<td>25.2</td>
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</tbody>
</table>

**OCTAVE Induction 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Tofacitinib 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFi-treated</td>
<td>0</td>
<td>12.0</td>
</tr>
<tr>
<td>TNFi-naive</td>
<td>8.5</td>
<td>22.1</td>
</tr>
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</table>

**Table**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFi-treated</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>TNFi-naive</td>
<td>32</td>
<td>254</td>
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<tr>
<td>TNFi-treated</td>
<td>9</td>
<td>57</td>
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<tr>
<td>TNFi-naive</td>
<td>56</td>
<td>222</td>
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<tr>
<td>TNFi-treated</td>
<td>0</td>
<td>65</td>
</tr>
<tr>
<td>TNFi-naive</td>
<td>28</td>
<td>234</td>
</tr>
<tr>
<td>TNFi-treated</td>
<td>4</td>
<td>47</td>
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<tr>
<td>TNFi-naive</td>
<td>43</td>
<td>195</td>
</tr>
</tbody>
</table>

Efficacy data are full analysis set with nonresponder imputation.

* P≤0.05 vs placebo. P values based on Cochran-Mantel-Haenszel chi-square test stratified by prior treatment with TNFi, corticosteroid use at baseline and geographic region.

Key Secondary Endpoint: Mucosal Healing at Week 8 By Prior TNFi Treatment

**OCTAVE Induction 1**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tofacitinib 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFi-treated</td>
<td>6.2</td>
<td>24.0</td>
</tr>
<tr>
<td>TNFi-naive</td>
<td>26.3</td>
<td>39.6</td>
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**OCTAVE Induction 2**

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Tofacitinib 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFi-treated</td>
<td>6.2</td>
<td>21.8</td>
</tr>
<tr>
<td>TNFi-naive</td>
<td>19.1</td>
<td>36.4</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>OCTAVE Induction 1</th>
<th>OCTAVE Induction 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4 61</td>
<td>4 51</td>
</tr>
<tr>
<td>N</td>
<td>65 254</td>
<td>65 234</td>
</tr>
</tbody>
</table>

* P≤0.05 vs placebo. P values based on Cochran-Mantel-Haenszel chi-square test stratified by prior treatment with TNFi, corticosteroid use at baseline, and geographic region.

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Primary Endpoint: Remission at Week 52 Based on Prior TNFi Failure Status (FAS, NRI, Central Read)

- **N1=** number of subjects in each group at baseline, and used as denominator in percentage calculation.
- BID= twice daily; CI= confidence interval; FAS= full analysis set; NRI= non-responder imputation; PBO= placebo; TNFi= tumor necrosis factor inhibitor.

<table>
<thead>
<tr>
<th>Prior TNFi Failure</th>
<th>Placebo (N=198)</th>
<th>Tofacitinib 5 mg BID (N=198)</th>
<th>Tofacitinib 10 mg BID (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>10</td>
<td>25.3</td>
<td>36.6</td>
</tr>
<tr>
<td></td>
<td>Δ=12.9</td>
<td>Δ=25.3</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>11.0</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>Δ=30.7</td>
<td>Δ=33.2</td>
<td></td>
</tr>
</tbody>
</table>

Placebo (N=198)  Tofacitinib 5 mg BID (N=198)  Tofacitinib 10 mg BID (N=197)
Key Secondary Endpoint:
Mucosal Healing at Week 52 (FAS, NRI)

*Mucosal healing: Mayo endoscopic subscore of 0 or 1*

<table>
<thead>
<tr>
<th>n</th>
<th>Central Read</th>
<th>Local Read</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diff. from PBO (95% CI)</td>
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</tr>
<tr>
<td>26</td>
<td>24.2 (16.0, 32.5)</td>
<td>29.3 (20.7, 37.9)</td>
</tr>
<tr>
<td>74</td>
<td>32.6 (24.2, 41.0)</td>
<td>38.2 (29.5, 46.8)</td>
</tr>
<tr>
<td>90</td>
<td>31</td>
<td>89</td>
</tr>
</tbody>
</table>

P values based on Cochran-Mantel-Haenszel chi-square test stratified by induction treatment and remission at baseline.

BID=twice daily; CI=confidence interval; FAS=full analysis set; NRI=non-responder imputation; PBO=placebo.
Most Common Treatment-Emergent AEs by Decreasing Frequency - Maintenance

TEAEs listed were those occurring with ≥5% frequency in either tofacitinib group

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Placebo N=198</th>
<th>Tofacitinib 5 mg BID N=198</th>
<th>Tofacitinib 10 mg BID N=196</th>
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</thead>
<tbody>
<tr>
<td>Colitis ulcerative, n (%)</td>
<td>71 (35.9)</td>
<td>36 (18.2)</td>
<td>29 (14.8)</td>
</tr>
<tr>
<td>Nasopharyngitis, n (%)</td>
<td>11 (5.6)</td>
<td>19 (9.6)</td>
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<tr>
<td>Headache, n (%)</td>
<td>12 (6.1)</td>
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<td>6 (3.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection, n (%)</td>
<td>7 (3.5)</td>
<td>13 (6.6)</td>
<td>12 (6.1)</td>
</tr>
<tr>
<td>Rash, n (%)</td>
<td>8 (4.0)</td>
<td>6 (3.0)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased, n (%)</td>
<td>4 (2.0)</td>
<td>6 (3.0)</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>2 (1.0)</td>
<td>4 (2.0)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Herpes zoster, n (%)</td>
<td>1 (0.5)</td>
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AE=adverse event; BID=twice daily; TEAE=treatment-emergent adverse event.
**Most Common Treatment-Emergent AEs by Decreasing Frequency - Maintenance**

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AE=adverse event; BID=twice daily; TEAE=treatment-emergent adverse event.
Upadacitinib: CELEST: Co-primary endpoints:
Clinical remission based on PRO &
endoscopic remission (NRI)

Endoscopic remission: SES-CD ≤ 4 and ≥2 point reduction vs. baseline (BL) and no subscore > 1 in any individual variable
Clinical remission: average daily very soft or liquid SF ≤ 1.5 and not worse than baseline AND average daily AP ≤ 1.0 and not worse than Baseline

*p<0.1; **p<0.05; ***p<.01

UK/EYV/1803/0027k April 2018
†Upadacitinib not licensed for use in IBD in the UK
Primary Endpoint: Clinical remission (Crohn’s Disease Activity Index <150)

- Filgotinib* 200 mg (N=111)
- Placebo (N=37)

Patients in clinical remission (%)

Weeks

Fitzroy

Vermiere et al. Lancet 2016

*Filgotinib not licensed for use in IBD in the UK
*products not licensed for use in IBD in the UK


UK/EYV/1803/0027k April 2018
Imprint tissue specific lymphocyte trafficking
Lymphocyte egress
Gut specific lymphocyte trafficking
Ozanimod: Induction and maintenance results from a Phase II trial

Week 8

- **Response†**
  - Ozanimod 1.0 mg (n=67): 57.0%
  - Ozanimod 0.5 mg (n=65): 54.0%
  - Placebo (n=65): 37.0%
  - *p=0.02  p=0.06*

Week 32

- **Response†**
  - Ozanimod 1.0 mg (n=67): 51.0%
  - Ozanimod 0.5 mg (n=65): 35.0%
  - Placebo (n=65): 20.0%
  - *p<0.001  p=0.06  p=0.01  p=0.002  p=0.005  p=0.006*

- **Remission‡**
  - Ozanimod 1.0 mg (n=67): 21.0%
  - Ozanimod 0.5 mg (n=65): 26.0%
  - Placebo (n=65): 6.0%
  - *p=0.002  p=0.01  p=0.005  p=0.006*

- **Mucosal healing§**
  - Ozanimod 1.0 mg (n=67): 33.0%
  - Ozanimod 0.5 mg (n=65): 32.0%
  - Placebo (n=65): 12.0%
  - *p=0.005  p=0.006*

†Reduction in Mayo score ≥3 and ≥30% from baseline, with a decrease in the rectal bleeding subscore of ≥1 or a subscore of ≤1; ‡Mayo score ≤2 with no subscore >1; §Endoscopy subscore ≤1. The primary outcome was clinical remission (Mayo Clinic score ≤2, with no subscore >1) at 8 weeks.

Differences in the primary outcome between the group that received 0.5 mg of ozanimod and the placebo group were not significant; therefore, the hierarchical testing plan deemed the analyses of secondary outcomes exploratory.

*Ozanimod not licensed for use in IBD in the UK*


UK/EYV/1803/0027k

April 2018
NB. This slide contains details of pipeline therapies that are not approved by regulatory authorities. Safety and efficacy have not been established.

Image source: Lees C
QUESTIONS?