The experience with tofacitinib in Humanitas IBD center, from theory to clinical practice

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Conflicts of Interest

- Consultancy fees from AbbVie, Allergan, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring Pharmaceuticals Inc., Gilead, Hospira, Janssen, Johnson & Johnson, MSD, Mundipharma, Pfizer, Roche, Sandoz, Takeda, TiGenix, UCB Inc., and Vifor.

- “The opinions expressed in this presentation belong to the presenter and do not necessarily reflect the views of the company. For all medicinal products mentioned, please refer to the approved Summaries of Product Characteristics”
FAQs in IBD clinic at tofacitinib launch

- How should we use a new drug once we have it in the clinic?
- What are the differentiators for a new drug?
What are the decision drivers?

- Disease/patient features
- Treatment strategies
- Positioning
- Data at launch
What are the decision drivers?

- Disease/patient features
- Treatment strategies
- Positioning
- Data at launch
### UC clinical development programme

<table>
<thead>
<tr>
<th>Study Name/ Number</th>
<th>Objective</th>
<th>Endpoints</th>
<th>Duration</th>
<th>Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 2</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A3921063(^1)</td>
<td>Dose-finding study to find optimal dose for Phase 3</td>
<td>Primary endpoint: clinical response at Week 8</td>
<td>8 weeks</td>
<td>September 2010</td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td></td>
<td></td>
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</tbody>
</table>
| OCTAVE Induction 1\(^2,3\) (A3921094) | Assess the efficacy and safety of tofacitinib as induction therapy for UC | Primary endpoint: remission at Week 8  
Key secondary endpoint: mucosal healing at Week 8 | 8 weeks* | May 2015 |
| OCTAVE Induction 2\(^3,4\) (A3921095) | Assess the efficacy and safety of tofacitinib as induction therapy for UC | Primary endpoint: remission at Week 8  
Key secondary endpoint: mucosal healing at Week 8 | 8 weeks* | May 2015 |
| OCTAVE Sustain\(^5,6\) (A3921096) | Assess the efficacy and safety of tofacitinib as maintenance therapy for UC | Primary endpoint: remission at Week 52  
Key secondary endpoints: mucosal healing at Week 52 and sustained steroid-free remission\(^1\) at Week 52 | 52 weeks* | May 2016 |
| OCTAVE Open\(^7\) (A3921139) | Open-label LTE study to assess the long-term use of tofacitinib | Primary endpoint: Safety measured by number of reported AEs | >12 months (ending with first market authorisation) | July 2018 (estimated) |

Final complete efficacy assessment at Week 8/52; treatment continued up to Week 9/53.

* Among subjects in remission at baseline.

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**The tofacitinib clinical development programme in UC comprises a phase 2 dose-finding trial, two identical phase 3 induction studies, a phase 3 maintenance study, and a long-term extension study.**

AEs, adverse events; LTE, long-term extension; UC, ulcerative colitis.
The OCTAVE Phase 3 program for UC consists of two identical induction studies (OCTAVE Induction 1 and 2), a maintenance study (OCTAVE Sustain), and a long-term extension study (OCTAVE Open).

- **OCTAVE Induction 1**
  - **Randomisation**: 10 mg BID, Placebo
  - **Assessment**: 8 weeks*, N=598 (4:1)

- **OCTAVE Induction 2**
  - **Randomisation**: 10 mg BID, Placebo
  - **Assessment**: 8 weeks*, N=541 (4:1)

- **OCTAVE Sustain**
  - **Randomisation**: Responders†
  - **Assessment**: 10 mg BID, 5 mg BID, Placebo
  - **Enrolment**: 52 weeks*, N=593 (1:1:1)

- **OCTAVE Open**
  - **Enrolment**: 5 mg BID‡, 10 mg BID‡
  - **Assessment**: Up to 1st approval, N=946

*Final complete efficacy assessment at Week 8/52. Treatment continued up to Week 9/53. †“Responders” refers to subjects who achieved clinical response during OCTAVE Induction 1 or 2. ‡Subjects in remission at Week 52 of OCTAVE Sustain were assigned to tofacitinib 5 mg BID. Subjects who completed 8 weeks of treatment in OCTAVE Induction 1 or 2 and were classified as nonresponders, and subjects who completed OCTAVE Sustain but did not meet remission or who withdrew from the study early due to treatment failure, were assigned to tofacitinib 10 mg BID.
Study design: OCTAVE Induction studies

Primary Objectives
1. Compare the efficacy of tofacitinib vs placebo in inducing remission (primary endpoint) and achieving mucosal healing (key secondary endpoint) in subjects with moderately to severely active UC after 8 weeks of treatment
2. Evaluate the safety and tolerability of tofacitinib after 8 weeks of treatment

Screening (3 weeks)¹,²

Randomisation (4:1)³

Tofacitinib 10 mg BID³
(OCTAVE Induction 1: N=476)
(OCTAVE Induction 2: N=429)

Placebo BID³
(OCTAVE Induction 1: N=122)
(OCTAVE Induction 2: N=112)

Double-blind, placebo-controlled treatment
8 weeks* 

Responders

OCTAVE Sustain

Non-responders

OCTAVE Open

Others

4-week follow-up

End of treatment

Follow-up 4 weeks

The primary endpoint was remission at Week 8

Subjects required to have prior failure or intolerance to ≥1 of the following therapies:³
- Oral or IV corticosteroids
- AZA or 6-MP
- TNFi

The induction studies initially included a tofacitinib 15 mg BID dose group, which was removed after a total of 22 subjects were randomised and completed the studies³

* Subjects received double-blind treatment for up to 9 weeks, with the final efficacy evaluation at Week 8.

OCTAVE Induction 1 and 2 were identically designed Phase 3 studies. The primary endpoint in OCTAVE Induction 1 and 2 was remission at Week 8.


6-MP, 6-mercaptopurine; AZA, azathioprine; BID, twice daily; TNF, tumour necrosis factor inhibitors; IV, intravenous
Significantly more patients achieved primary endpoint at Week 8 with tofacitinib vs placebo

Treatment effect was observed in TNFi-treated and TNFi-naïve patients (% difference from placebo [95% confidence intervals]):

- **OCTAVE Induction 1**: TNFi-treated (11.1 [6.0, 16.1]); TNFi-naïve (9.4 [-1.6, 20.5])
- **OCTAVE Induction 2**: TNFi-treated (12.0 [7.8, 16.1]); TNFi-naïve (13.5 [3.7, 23.4])

Data are full analysis set with non-responder imputation

**p<0.01; ***p<0.001 vs placebo (Cochran-Mantel-Haenszel chi-square test)
Primary endpoint: remission at week 8 by prior TNFi treatment

The treatment effect for remission was similar in patients who were TNFi treated and TNFi naive.

**OCTAVE Induction 1**

- TNFi treated: 1.5 (Δ=11.1)**
- TNFi naive: 12.6

**OCTAVE Induction 2**

- TNFi treated: 0 (Δ=12.0)**
- TNFi naive: 8.5 (Δ=13.5)**

*P≤0.05

<table>
<thead>
<tr>
<th></th>
<th>OCTAVE Induction 1</th>
<th>OCTAVE Induction 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFi treated</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TNFi naive</td>
<td>32</td>
<td>28</td>
</tr>
</tbody>
</table>

For Tofacitinib 10 mg BID versus Placebo:

- OCTAVE Induction 1: n=1, N=65
- OCTAVE Induction 2: n=9, N=254


BID, twice daily; TNFi, tumour necrosis factor inhibitors
Tofacitinib had a significant effect vs placebo on mucosal healing at Week 8

Treatment effect was observed in TNFi-treated and TNFi-naïve patients (% difference from placebo [95% confidence intervals]):

- **OCTAVE Induction 1:**
  - TNFi-treated: 17.9 [10.0, 25.77]
  - TNFi-naïve: 13.3 [0.2, 26.4]

- **OCTAVE Induction 2:**
  - TNFi-treated: 15.6 [7.8, 23.5]
  - TNFi-naïve: 17.3 [4.1, 30.4]

Data are full analysis set with non-responder imputation

**p<0.01; ***p<0.001 vs placebo (Cochran-Mantel-Haenszel chi-square test)
Key secondary endpoint: mucosal healing at week 8 by prior TNFi treatment

P values based on Cochran-Mantel-Haenszel chi-square test stratified by prior treatment with TNFi, corticosteroid use at baseline, and geographic region. Efficacy data are full analysis set with nonresponder imputation (central read).

2. A3921094 and A3921095 Study Report Output; Table 14.2.3.3.

BID, twice daily; TNFi, tumour necrosis factor inhibitors
Primary endpoint: remission at Week 52 (FAS, NRI; central read)

- A significantly greater proportion of patients receiving tofacitinib were in remission at Week 52 vs patients receiving placebo

Data are FAS with NRI, central read. FAS consisted of all randomized subjects.

p<0.001 vs placebo; calculated by Cochran-Mantel-Haenszel chi-square test.

Remission is defined as total Mayo score ≤2; no subscore >1; rectal bleeding subscore of 0.

BID, twice daily; CI, confidence interval; Diff., difference; FAS, full analysis set; NRI, non-responder imputation; N, total number of patients in the analysis set; n, number of patients meeting endpoint criteria.
Primary endpoint: Remission at week 52 by prior TNFi treatment

Efficacy data are full analysis set with non-responder imputation (central read).

<table>
<thead>
<tr>
<th>n</th>
<th>11</th>
<th>24</th>
<th>37</th>
<th>11</th>
<th>44</th>
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<tbody>
<tr>
<td>N</td>
<td>92</td>
<td>90</td>
<td>101</td>
<td>106</td>
<td>108</td>
<td>96</td>
</tr>
</tbody>
</table>

A3921096 Study Report Output; Tables 14.2.2.4 and 14.2.2.5.

BID, twice daily; TNFi, tumour necrosis factor inhibitor.
Mucosal healing at Week 52 was observed in a significantly greater proportion of patients receiving tofacitinib vs patients receiving placebo.

Data are FAS with NRI, central read. FAS consisted of all randomized subjects p<0.001 vs placebo; calculated by Cochran-Mantel-Haenszel chi-square test.

Mucosal healing defined as Mayo endoscopic subscore of 0 or 1.

BID, twice daily; CI, confidence interval; Diff., difference; FAS, full analysis set; NRI, non-responder imputation; N, total number of patients in the analysis set; n, number of patients meeting endpoint criteria.
Key secondary endpoint: Mucosal healing at week 52 by prior TNFi treatment

<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>TNFi treated</td>
<td>13.0</td>
<td>32.2</td>
<td>39.6</td>
</tr>
<tr>
<td>TNFi naive</td>
<td>13.2</td>
<td>41.7</td>
<td>52.1</td>
</tr>
<tr>
<td>Δ</td>
<td>19.2</td>
<td>26.6</td>
<td>28.5</td>
</tr>
<tr>
<td>Δ</td>
<td></td>
<td></td>
<td>38.9</td>
</tr>
</tbody>
</table>

Efficacy data are full analysis set with non-responder imputation (central read).

A3921096 Study Report Output; Tables 14.2.3.4 and 14.2.3.5.

BID, twice daily; TNFi, tumour necrosis factor inhibitor.
FAQ in IBD clinic at tofacitinib launch

• Before or after anti-TNF?

There is definitely a place for tofacitinib use as a first-line biologic after failure of, or contraindications to, a conventional therapy, beside second line after failure on anti-TNFs.
What are the decision drivers?

- Disease/patient features
- Treatment strategies
- Positioning
- Data at launch
What sources are available to inform positioning of a new drug vs competitors?

There is a paucity of head-to-head trials that inform clinicians on the appropriate efficacious and safe treatment regimens for IBD.
Head-to-head trials in other IMIDs

Moderate-to-severe rheumatoid arthritis
- Abatacept (CTLA4Ig) is not inferior to adalimumab (anti-TNF)
- Adalimumab (anti-TNF) is superior to pateclizumab\(^a\) (anti-lymphotoxin-α)
- Certolizumab pegol (anti-TNF) is not inferior to adalimumab (anti-TNF)
- Tofacitinib (anti-JAK) is not inferior to adalimumab (anti-TNF)

Moderate-to-severe (plaque) psoriasis
- Ustekinumab (anti-IL-12/23) is superior to etanercept (anti-TNF)
- Secukinumab (anti-IL-17A) is superior to etanercept (anti-TNF)
- Secukinumab (anti-IL-17A) is superior to ustekinumab (anti-IL-12/23)
- Ixekizumab (anti-IL-17A) is superior to etanercept (anti-TNF) and superior to ustekinumab (anti-IL-12/23)
- Guselkumab is superior to adalimumab and superior to ustekinumab in UST-IR
- Risankizumab\(^b\) (anti-IL-23) is superior to ustekinumab (anti-IL-12/23)

\(^a\) Currently not indicated for the treatment of rheumatoid arthritis.
\(^b\) Currently not indicated for the treatment of psoriasis.

CTLA4, cytotoxic T-lymphocyte-associated protein 4; IMID, immune-mediated inflammatory disease; JAK, Janus kinase, UST-IR, ustekinumab immediate release.
Head-to-head trials of biologics with different MoAs in ulcerative colitis are underway


MoAs, mechanisms of action.

- Vedolizumab vs adalimumab
  - VARSITY Maintenance: 52 weeks
  - HIBISCUS 1&2 Induction: 10 weeks
  - EXPEDITION Maintenance: 54 weeks

- Etrolizumab vs adalimumab
  - Etrolizumab vs infliximab
  - Etrolizumab vs adalimumab

- Brazikumab vs vedolizumab
  - GARDENIA Maintenance: 54 weeks

Estimated primary completion date

- VARSITY: February 2019
- HIBISCUS 1&2: October 2019
- EXPEDITION: February 2020
- GARDENIA: March 2020
What have we learned from indirect comparisons of ulcerative colitis clinical trials?

<table>
<thead>
<tr>
<th>Year</th>
<th>RCTs, n</th>
<th>Endpoints (Population)</th>
<th>Comparison</th>
<th>Comparators</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>7</td>
<td>Induction and maintenance, safety (no separate analysis for biologic-naïve vs prior anti-TNF exposure pts)</td>
<td>Biologic vs PBO; biologic vs biologic</td>
<td>Infliximab, Adalimumab, Golimumab, Vedolizumab</td>
</tr>
<tr>
<td>2016</td>
<td>7</td>
<td>Induction and maintenance (analysis for biologic-naïve vs prior anti-TNF exposure)</td>
<td>Biologic vs PBO; biologic vs biologic</td>
<td>Infliximab, Adalimumab, Golimumab, Vedolizumab</td>
</tr>
<tr>
<td>2017</td>
<td>5</td>
<td>Mucosal healing (no separate analysis for biologic-naïve vs prior anti-TNF exposure pts)</td>
<td>Biologic vs PBO; biologic vs biologic</td>
<td>Infliximab, Adalimumab, Golimumab, Vedolizumab</td>
</tr>
<tr>
<td>2018</td>
<td>15</td>
<td>Induction and maintenance, safety (analysis only for pts without prior anti-TNF exposure)</td>
<td>Drug vs PBO; drug vs drug</td>
<td>Infliximab, Adalimumab, Golimumab, Vedolizumab</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Induction and maintenance, safety (analysis for biologic-naïve vs prior anti-TNF exposure)</td>
<td>Drug vs PBO; drug vs drug</td>
<td>Infliximab, Adalimumab, Golimumab, Vedolizumab</td>
</tr>
</tbody>
</table>

PBO, placebo; pts, patients; RCTs, randomised controlled trials, TNF, tumour necrosis factor.


Head-to-head trials are needed to inform clinical decision-making with greater confidence.
### Induction efficacy in biologic-naïve UC patients: Tofacitinib and all biologics studied were superior to placebo

#### Induction of clinical remission

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Study or Subgroup</th>
<th>OR [95% CI]*</th>
<th>OR [95% CI]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab vs. placebo</td>
<td>Reinisch ULTRA 1, ITT-A3 (2011)</td>
<td>2.23 [1.06, 4.67]</td>
<td>2.98 [0.91, 9.74]</td>
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<tr>
<td></td>
<td>Reinisch ULTRA 1, ITT-E (2011)</td>
<td>2.19 [1.14, 4.19]</td>
<td>0.86 [0.34, 2.18]</td>
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<tr>
<td></td>
<td>Sandborn ULTRA 2 (2012)</td>
<td>2.23 [1.06, 4.67]</td>
<td>2.98 [0.91, 9.74]</td>
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<tr>
<td></td>
<td>Suzuki (2014)</td>
<td>1.92 [1.29, 2.86]</td>
<td>1.89 [1.19, 3.00]</td>
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<tr>
<td></td>
<td>Fixed effect model</td>
<td>2.23 [1.06, 4.67]</td>
<td>2.98 [0.91, 9.74]</td>
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<tr>
<td></td>
<td>Random effects model</td>
<td>1.92 [1.29, 2.86]</td>
<td>1.89 [1.19, 3.00]</td>
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<tr>
<td>Golimumab vs. placebo</td>
<td>Sandborn PURSUIT-SC Ph2 (2014)</td>
<td>2.81 [1.69, 4.69]</td>
<td>2.80 [1.67, 4.67]</td>
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<td></td>
<td>Sandborn PURSUIT-SC Ph2 add. (2014)</td>
<td>2.81 [1.69, 4.69]</td>
<td>2.80 [1.67, 4.67]</td>
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<tr>
<td></td>
<td>Sandborn PURSUIT-SC Ph3 (2014)</td>
<td>2.81 [1.69, 4.69]</td>
<td>2.80 [1.67, 4.67]</td>
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<td>Fixed effect model</td>
<td>2.81 [1.69, 4.69]</td>
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<tr>
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<td>Random effects model</td>
<td>2.81 [1.69, 4.69]</td>
<td>2.80 [1.67, 4.67]</td>
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<tr>
<td></td>
<td>Fixed effect model</td>
<td>3.81 [1.74, 5.79]</td>
<td>4.03 [2.75, 5.89]</td>
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<td></td>
<td>Random effects model</td>
<td>3.81 [1.74, 5.79]</td>
<td>4.03 [2.75, 5.89]</td>
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<tr>
<td>Tofacitinib vs. placebo</td>
<td>Sandborn OCTAVE Induction 1 (2017)</td>
<td>1.80 [0.83, 3.90]</td>
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<td>Sandborn OCTAVE Induction 2 (2017)</td>
<td>1.80 [0.83, 3.90]</td>
<td>3.04 [1.03, 8.95]</td>
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<td></td>
<td>Sandborn Study A39221063 (2012)</td>
<td>1.80 [0.83, 3.90]</td>
<td>3.04 [1.03, 8.95]</td>
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<tr>
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<td>2.47 [1.40, 4.34]</td>
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<tr>
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<td>Random effects model</td>
<td>2.47 [1.40, 4.34]</td>
<td>2.47 [1.40, 4.34]</td>
</tr>
<tr>
<td></td>
<td>Fixed effect model</td>
<td>4.26 [1.58, 11.52]</td>
<td>4.26 [1.58, 11.52]</td>
</tr>
<tr>
<td></td>
<td>Random effects model</td>
<td>4.26 [1.58, 11.52]</td>
<td>4.26 [1.58, 11.52]</td>
</tr>
</tbody>
</table>

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- 15 randomised controlled trials included in network meta-analysis (N=3130)
- All the treatments under evaluation (tofacitinib, adalimumab, golimumab, infliximab and vedolizumab) demonstrated superiority over placebo

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General safety

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>Induction Cohort¹</th>
<th>Maintenance Cohort¹,²</th>
<th>Overall Cohort¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=282)</td>
<td>Tofacitinib 10 mg BID (N=938)</td>
<td>Placebo (N=198)</td>
</tr>
<tr>
<td>Patients with AEs</td>
<td>155 (55.0)</td>
<td>515 (54.9)</td>
<td>149 (75.3)</td>
</tr>
<tr>
<td>Patients with SAEs</td>
<td>18 (6.4)</td>
<td>36 (3.8)</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td>Patients with severe AEs¹</td>
<td>15 (5.3)</td>
<td>38 (4.1)</td>
<td>19 (9.6)</td>
</tr>
<tr>
<td>Discontinuations due to AEs</td>
<td>14 (5.0)</td>
<td>36 (3.8)</td>
<td>37 (18.7)</td>
</tr>
</tbody>
</table>

Most frequently occurring AEs ≥10% of patients

- Headache
  - Placebo (N=282): 19 (6.7)
  - Tofacitinib 10 mg BID (N=938): 73 (7.8)
- Nasopharyngitis
  - Placebo (N=198): 11 (5.6)
  - Tofacitinib 5 mg BID (N=198): 19 (9.6)
- Worsening UC
  - Placebo (N=196): 71 (35.9)
  - Tofacitinib 10 mg BID (N=196): 36 (18.2)

Most frequent SAE – worsening UC

- Placebo: 9 (3.2)
- Tofacitinib 10 mg BID: 14 (1.5)

Only events occurring within 28 days after the last dose are included in this table for calculation of proportion; AEs and SAEs were coded using MedDRA, version 19.0; severe AE intensity was described by the investigators. *Data for the Overall Cohort are n (%) of patients with dose reduction or temporary discontinuation due to AE.*

- In the Induction and Maintenance Cohorts, the most frequent reason for discontinuation was insufficient clinical response, including the AE of worsening UC.
- In Cohort 3, the SOCs in which AEs most frequently occurred (all causality) were Gastrointestinal disorders SOC and Infections and infestations SOC.

Safety events of special interest

- Infections
  - Serious infections
  - Herpes zoster
  - Opportunistic infections

- Malignancies

- Cardiovascular events

- Gastrointestinal perforations
Risk of herpes zoster associated with treatments in patients with IBD

Retrospective, nested case-control study using procedural and retail pharmacy claims data from IMS LifeLink® Information Assets-Health Plan Claims Database from January 1997 through December 2009 to assess the independent effects of medication use on herpes zoster risk among patients with IBD.

Adjusted for health care utilization, comorbidities, 5-ASA, and corticosteroid use as appropriate. Thiopurine defined as mercaptopurines or azathioprine. Biologic defined as infliximab, adalimumab, or certolizumab pegol. Combination therapy defined as both thiopurine and biologic.

Incidence rates of herpes zoster (shingles) (serious and non-serious)

Events are counted up to 28 days (except subjects that are Ongoing in A3921139) beyond the last dose. PY: Total follow up time calculated up to the earliest of: day of the first event, time to data cutoff or progression to next study, or time to last dose + 28 days. Exact Poisson (adjusted for PY) CI are provided for the crude IR.

Herpes zoster events in Cohort 3:
clinical characterisation

Herpes Zoster Events by Number of Dermatomes and OI Categories

- 1 or 2 Adjacent Dermatomes: 73.9%
- Multi-dermatomal: 17.4%
- Disseminated: 8.7%

Herpes Zoster Events by Cutaneous Involvement

- Cutaneous Only: 95.7%
- Ocular: 2.9%
- Meningitis: 1.4%

n=51, 12, 6
n=66, 2, 1

HZ, herpes zoster.

Pfizer Data on File
HDL-C, LDL-C, and LDL-C/HDL-C Ratio Over Time (Observed): OCTAVE Sustain

BID=twice daily; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; SD=standard deviation.
A3921096 Study Report Output; Table 14.3.4.1.6. Data as of June 2016.
Treatment With Tofacitinib Was Associated With Early, Nonprogressive Increases in Lipid Parameters That Were Responsive to Statin Treatment

- Treatment with tofacitinib was associated with changes in lipid parameters*:
  - No change in the LDL/HDL ratio
  - Maximum effects generally observed within 6 weeks and responsive to statin treatment

* Mean percent change from baseline, observed in patients in the LTE. Data as of 2016. † Beyond Month 90, fewer than 100 patients are included in the analysis.

HDL=high-density lipoprotein; LDL=low-density lipoprotein; TC=total cholesterol.
What are the decision drivers?

- Disease/patient features
- Treatment strategies
- Positioning
- Data at launch
let’s move from theory to practice
Patient case study: John, 34 years

- **2013:** E3 UC (up to hepatic flexure)
  - Mild activity at diagnosis
  - Oral 5-ASA 3–4.5 g ± rectal 5-ASA 1–4 g
  - One course of oral steroids

- **2014:** azathioprine 150–200 mg/day (~2.5 mg/kg/day)
  - Disease still active after 3 months’ treatment
  - Visits hospital for consultation

- **pMayo = 8**
  - 5–6 BMs/day, bloody diarrhoea, tenesmus, urgency, cramps, no fever
  - Hb = 11.5 g/dL, CRP = 24.7 mg/L

- Latent TB screening: negative
- CMV negative (IHC and PCR)
- Sigmoidoscopy (eMayo = 3)

E3=extensive colitis; 5-ASA=5-aminosalicylic acid; BM=bowel movement; CMV=cytomegalovirus; CRP=C-reactive protein; eMayo=endoscopic Mayo subscore; Hb=haemoglobin; IHC=immunohistochemistry; PCR=polymerase chain reaction; pMayo=partial Mayo score; TB=tuberculosis
How do we choose which drug to prescribe?

Lack of head-to-head trials...

Multiple options for patients...
Benefits of tofacitinib treatment in moderate-to-severe ulcerative colitis

Rapid response: Significant improvement in symptoms versus placebo evident by Day 3¹

Stool frequency

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Tofacitinib 10 mg BID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.11</td>
<td>-0.11</td>
</tr>
<tr>
<td>1</td>
<td>-0.27</td>
<td>-0.27</td>
</tr>
<tr>
<td>2</td>
<td>-0.30</td>
<td>-0.30</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rectal bleeding

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Tofacitinib 10 mg BID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.14</td>
<td>-0.27</td>
</tr>
<tr>
<td>1</td>
<td>-0.27</td>
<td>-0.27</td>
</tr>
<tr>
<td>2</td>
<td>-1.06</td>
<td>-1.06</td>
</tr>
<tr>
<td>15</td>
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<td></td>
</tr>
</tbody>
</table>

Number of daily bowel movements

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Tofacitinib 10 mg BID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.30</td>
<td>-0.30</td>
</tr>
<tr>
<td>1</td>
<td>-1.06</td>
<td>-1.06</td>
</tr>
<tr>
<td>2</td>
<td>-2.05</td>
<td>-2.05</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.01 vs placebo; **P<0.0001 vs placebo.
BID=twice daily; LS=least squares; SE=standard error.
Benefits of tofacitinib treatment in moderate-to-severe ulcerative colitis\(^1\)

- Short serum half-life
- Immunogenicity not expected

<table>
<thead>
<tr>
<th>Characteristics of biologic and small molecule therapies(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biologics</strong></td>
</tr>
<tr>
<td>Chemical composition</td>
</tr>
<tr>
<td>Administration</td>
</tr>
<tr>
<td>Molecular size</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Target</td>
</tr>
<tr>
<td>Immunogenicity</td>
</tr>
</tbody>
</table>

kDa = kilodalton.
Benefits of tofacitinib treatment in moderate-to-severe ulcerative colitis

- Potential first-line advanced therapy after 5-ASAs and steroids
- Effective in patients previously treated with TNF inhibitors
- Experience in RA

5-ASA=5-aminosalicylic acid; RA=rheumatoid arthritis; TNF=tumour necrosis factor.
Prior TNFi failure: Remission at Week 8 and Week 52

**Week 8***

- Without prior TNFi failure:
  - Placebo: 12% (13/110)
  - Tofacitinib 5 mg BID: 24% (106/440)
  - Tofacitinib 10 mg BID: 1% (1/124)

- With prior TNFi failure:
  - Placebo: 11% (53/465)

**Week 52**

- Without prior TNFi failure:
  - Placebo: 11% (12/109)
  - Tofacitinib 5 mg BID: 42% (48/115)
  - Tofacitinib 10 mg BID: 44% (46/104)

- With prior TNFi failure:
  - Placebo: 11% (10/89)
  - Tofacitinib 5 mg BID: 24% (20/83)
  - Tofacitinib 10 mg BID: 37% (34/93)

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*Data combined from OCTAVE Induction study 1 and 2. BID=twice daily; TNFi=tumour necrosis factor inhibitor.
1. XELJANZ SmPC August 2018. Pfizer Ltd; 2018.
Prior TNFi failure: Mucosal healing at Week 8 and Week 52

Week 8†

Week 52

Placebo
Tofacitinib 5 mg BID
Tofacitinib 10 mg BID

*Improvement in mucosal appearance determined endoscopically/by central endoscopy read; †Data combined from OCTAVE Induction study 1 and 2. BID=twice daily; TNFi=tumour necrosis factor inhibitor.

1. XELJANZ SmPC August 2018. Pfizer Ltd; 2018.
• One of the very first patients included in the OCTAVE trials

• Induction with tofacitinib 10 mg BID

- Clinical improvement observed by Day 5
- Continued remission since 2014 at tofacitinib 5 mg BID
- No steroid use since then; repeat blood tests every 3 months

BID=twice daily.
Advantages of tofacitinib use in patients with ulcerative colitis
Advantages of tofacitinib use in patients with ulcerative colitis

Oral administration 1

Rapid absorption time 2

Advantages of tofacitinib

Advantages of tofacitinib use in patients with ulcerative colitis

Oral administration

Rapid absorption time

Short serum half-life

Advantages of tofacitinib use in patients with ulcerative colitis

- Oral administration
- Rapid absorption time
- Short serum half-life
- No immunogenicity

Advantages of tofacitinib use in patients with ulcerative colitis

- Oral administration
- Rapid absorption time
- Short serum half-life
- Potential firstline therapy after 5-ASA and steroids
- No immunogenicity

Advantages of tofacitinib use in patients with ulcerative colitis

- Oral administration
- Rapid absorption
- Short serum half-life
- Effective in patients previously treated with anti-TNF agents
- Potential firstline therapy after 5-ASA and steroids
- No immunogenicity

Advantages of tofacitinib use in patients with ulcerative colitis

- Oral administration
- Rapid absorption time
- Short serum half-life
- No immunogenicity
- Effective in patients previously treated with anti-TNF agents
- Potential first-line therapy after 5-ASA and steroids
- Potential for use in mild, moderate, and severe UC

Advantages of tofacitinib use in patients with ulcerative colitis

- Oral administration
- Rapid absorption time
- Short serum half-life
- Experience in RA
- Effective in patients previously treated with anti-TNF agents
- Potential first-line therapy after 5-ASA and steroids
- No immunogenicity

Potential for use in mild moderate, and severe UC

BACK UP SLIDES
Deep vein thrombosis (DVT) and pulmonary embolism (PE) in general population

- Reported to occur in 1-2 in 1000 patients in the general population\(^1\)-\(^5\)
- The risk with increasing age or with fracture of lower extremities, immobilisation, joint replacement surgery, major general surgery, major trauma, malignancy, heart or respiratory failure, pregnancy, history of VTE, hormone replacement therapy, oral contraceptive use, obesity, smoking and inherited thrombophilias.\(^1,6\)

Risk of DVT and PE in ulcerative colitis

- In a review of the Manitoba Health administrative database, the incidence rates of DVT and PE for patients with UC were 0.30 and 0.20 per 100 patient-years, respectively.\(^7\)
- From Danish Civil Registration System, an increased risk of DVT and PE in patients with ulcerative colitis as noted by the following hazard ratios: DVT (1.8 [95% CI: 1.6-2.0]); unprovoked* DVT (1.5 [95% CI: 1.3-1.7]); PE (2.0 [95% CI: 1.8-2.2]); and unprovoked PE (1.6 [95% CI: 1.4-1.9]). The IRs of DVT and PE for patients with UC in this analysis were 0.14 and 0.10 events per 100 patient-years, respectively.\(^8\)

References:
Signs and Symptoms for Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

- **Signs and Symptoms for DVT**¹,²
  - Asymmetrical swelling, warmth, or pain in the extremity
  - Red or discolored skin on the extremity

- **Signs and Symptoms for PE**³
  - Sudden shortness of breath or difficulty breathing
  - Chest pain or pain in the back
  - Coughing up blood
  - Tachycardia
  - Excessive sweating
  - Cyanosis

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# Deep Vein Thrombosis and Pulmonary Embolism in Tofacitinib UC Development Program

<table>
<thead>
<tr>
<th></th>
<th>Induction P2P3</th>
<th>Maintenance P3</th>
<th>All Tofacitinib doses (P2P3LTE)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 282, PY=45)</td>
<td>Tofacitinib 10 mg BID (N = 938, PY=156)</td>
<td>Placebo (N = 198, PY=100)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N = 198, PY=100)</td>
<td>Tofacitinib 5 mg BID (N = 198, PY=146)</td>
<td>Tofacitinib 10 mg BID (N = 196, PY=154)</td>
</tr>
<tr>
<td></td>
<td>Tofacitinib 5 mg BID (N=197, PY=596)</td>
<td>Predominant Tofacitinib 5 mg BID (N=960, PY=1801)</td>
<td>Predominant Tofacitinib 10 mg BID (N=1157, PY=2404)</td>
</tr>
<tr>
<td>Subjects with Deep Vein Thrombosis n (%)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>IR (95% CI)</td>
<td>1.99 (0.05, 11.07)</td>
<td>0.00 (0.00, 2.22)</td>
<td>0.97 (0.02, 5.39)</td>
</tr>
<tr>
<td>Subjects with Pulmonary Embolism n (%)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>IR (95% CI)</td>
<td>1.98 (0.05, 11.04)</td>
<td>0.00 (0.00, 2.22)</td>
<td>0.98 (0.02, 5.44)</td>
</tr>
</tbody>
</table>


*Data cut-off date September 2018
Deep Vein Thrombosis and Pulmonary Embolism in Tofacitinib UC Development Program Treated with Tofacitinib

- **U.S. Prescribing Information:** Four cases of pulmonary embolism were reported in patients taking Xeljanz 10 mg twice daily within the tofacitinib UC development program, including one fatality in a patient with advanced cancer.1*

- **OCTAVE Open**
  - **Deep vein thrombosis:**
    - 58 years of age at DVT event (PD tofacitinib 10mg BID)
      - 1149 days following the first dose of tofacitinib
      - Following a long haul flight and management of an infected leg wound sustained in a recent motorbike accident
  - **Pulmonary embolism:**
    - 70 years of age at PE event (PD Tofacitinib 10mg BID)
      - 383 days following the first dose of tofacitinib with cholangiocarcinoma and metastases to the peritoneum
      - Died due to PE
    - 57 years of age at PE event (PD Tofacitinib 10mg BID)
      - 236 days following the first dose of tofacitinib with prior phlebothrombosis and stroke
    - 25 years of age at PE event (PD Tofacitinib 10mg BID)
      - 216 days following the first dose of tofacitinib with prior DVT and PE
    - 21 years of age at PE event (PD tofacitinib 10mg BID)
      - 569 days following the first dose of tofacitinib
      - Receiving oral contraceptives for dysfunctional uterine bleeding

Reference:

*Data cut-off date July 2016; **Data cut-off date September 2018
Mortality in UC Tofacitinib Development Program Treated with Tofacitinib

<table>
<thead>
<tr>
<th>Subjects with events</th>
<th>Induction P2P3</th>
<th>Maintenance P3</th>
<th>All Tofacitinib doses (P2P3LTE)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N = 282, PY=51)</td>
<td>Tofacitinib 10 mg BID (N = 938, PY=166)</td>
<td>Placebo (N = 198, PY=103)</td>
<td>Tofacitinib 5 mg BID (N = 198, PY=149)</td>
</tr>
<tr>
<td>n (%)</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>IR (CI)</td>
<td>0.00 (0.00, 7.30)</td>
<td>0.60 (0.02, 3.35)</td>
<td>0.00 (0.00, 3.57)</td>
</tr>
</tbody>
</table>

Listing of all deaths
- **Aortic Dissection:** 40-year-old male died on Day 31; last known does on Day 31
- **Hepatic angiosarcoma:** 54-year-old male died on Day 232; last known does on Day 187
- **Acute myeloid leukemia:** 54-year-old male died on Day 398; last known does on Day 347
- **Pulmonary embolism complicating cholangiocarcinoma with metastases:** 70-year-old male died on Day 384; last known does on Day 378
- **Malignant Melanoma:** 66-year-old male died on Day 1518; last known does on Day 1359


*Data cut-off date September 2018