Long-term efficacy of tofacitinib in patients who received extended induction therapy: Results of the OCTAVE Open study for tofacitinib delayed responders

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Background

- Tofacitinib is an oral, small molecule JAK inhibitor for the treatment of UC
- The efficacy and safety of tofacitinib was shown in three Phase 3, randomised, placebo-controlled trials in patients with moderately to severely active UC\(^1\)
- Patients who did not achieve a clinical response\(^a\) in OCTAVE Induction 1 and 2 could enter an ongoing, Phase 3, multicentre, open-label, long-term extension study and continue to receive tofacitinib 10 mg BID\(^2\) – ie extended induction (16 weeks)

**Objective:** To present efficacy up to 3 years for induction non-responder patients who responded to extended induction with tofacitinib 10 mg BID


\(^a\)Clinical response, a decrease from induction baseline total Mayo score of ≥3 points and ≥30%, with an accompanying decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1 [centrally read]. BID, twice daily; UC, ulcerative colitis
Delayed responders

- 429 induction non-responder patients entered OCTAVE Open, of which 295 received tofacitinib 10 mg BID during induction.
- At Week 8 of OCTAVE Open – ie after a total of 16 weeks induction (extended induction)
  - Patients who were still non-responders were required to discontinue, as per the protocol.
  - Patients who achieved a clinical response - ie delayed responders - continued on tofacitinib 10 mg BID in OCTAVE Open (N=148).

- Efficacy was evaluated for continue tofacitinib treatment in OCTAVE Open for these delayed responders.

- Safety data presented for the overall UC clinical trial program.

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**OCTAVE Induction 1 and 2**
(NCT01465763; NCT01458951)

- 8-weeks tofacitinib 10 mg BID
- Non-responders N=295

**OCTAVE Open**
(NCT01470612)

- Month 2 assessment
- Continue tofacitinib 10 mg BID
- Responders N=148
- Non-responders
- Discontinue as per protocol

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$^a$Patients received either placebo (N=234) or tofacitinib 10 mg BID (N=905) during OCTAVE Induction 1 and 2. Induction responders entered OCTAVE Sustain and received placebo, tofacitinib 5 or 10 mg BID for 52 weeks; 
$^b$Responders were defined as patients with a decrease from induction baseline total Mayo score of ≥3 points and ≥30%, with an accompanying decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1 [centrally read].

BID, twice daily
Baseline characteristics\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>16-week extended induction responders (delayed responders)(^b) (N=148)</th>
<th>8-week induction responders(^c) (N=523)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>54 (36.5)</td>
<td>230 (44.0)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>40.4 (13.5)</td>
<td>42.7 (13.9)</td>
</tr>
<tr>
<td>Duration of diagnosis (years), mean (SD)</td>
<td>8.8 (7.4)</td>
<td>8.5 (7.1)</td>
</tr>
<tr>
<td>Extent of disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctosigmoiditis</td>
<td>23 (15.5)</td>
<td>69 (13.2)(^d)</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>53 (35.8)</td>
<td>170 (32.6)(^d)</td>
</tr>
<tr>
<td>Extensive colitis/pancolitis</td>
<td>72 (48.6)</td>
<td>281 (53.9)(^d)</td>
</tr>
<tr>
<td>Prior TNFi failure, n (%)</td>
<td>85 (57.4)</td>
<td>236 (45.1)</td>
</tr>
<tr>
<td>Oral corticosteroid use at baseline, n (%)</td>
<td>50 (33.8)</td>
<td>259 (49.5)</td>
</tr>
<tr>
<td>Total Mayo score, mean (SD)</td>
<td>9.1 (1.4)</td>
<td>8.8 (1.4)</td>
</tr>
</tbody>
</table>

Clinical response was defined as patients with a decrease from induction baseline total Mayo score of \(\geq 3\) points and \(\geq 30\%\), with an accompanying decrease in rectal bleeding subscore of \(\geq 1\) point or an absolute rectal bleeding subscore of 0 or 1 [centrally read]. \(^a\)Per data from induction baseline; \(^b\)Patients who demonstrated a clinical response following 16 weeks of tofacitinib 10 mg BID; \(^c\)Patients who demonstrated a clinical response to 8 Weeks in OCTAVE Induction; \(^d\)N=521

BID, twice daily; N, number of patients in the analysis population; n, number of patients in the category; SD, standard deviation; TNFi, tumour necrosis factor inhibitor
Month 12 delayed responder patient responses were similar to Month 12 responses of 8-week induction responders who stayed on tofacitinib 10 mg BID in OCTAVE Sustain (41.0% remission; 46.2% mucosal healing; 61.8% clinical response).

Only patients who were in clinical response at Month 2 per central read of endoscopy are included in this analysis. Months 12, 24 and 36 data are based on local read endoscopy with non-responder imputation for missing data.

BID, twice daily; N1, number of patients who could have reached time point (based on enrolment dates and last non-missing total Mayo score); n, number of patients with the specified response within the given category; OLE, open-label, long-term extension; TNFi, tumour necrosis factor inhibitor.
## Safety in the tofacitinib UC clinical program

<table>
<thead>
<tr>
<th>Overall Cohort (Induction, maintenance, OLE)(^a)</th>
<th>Predominant dose tofacitinib 10 mg BID(^b) (N=956; 1538.3 PY)</th>
<th>Predominant dose tofacitinib 5 mg BID(^c) (N=201; 512.2 PY)</th>
<th>All tofacitinib treated patients (N=1157; 2050.5 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-causality AEs, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>784 (82.0)</td>
<td>185 (92.0)</td>
<td>969 (83.8)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>165 (17.3)</td>
<td>28 (13.9)</td>
<td>193 (16.7)</td>
</tr>
<tr>
<td>Dose reduction or temporary discontinuation due to AE</td>
<td>66 (6.9)</td>
<td>23 (11.4)</td>
<td>89 (7.7)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (0.2)</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td><strong>AEs of special interest, IR (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious infection</td>
<td>2.02 (1.38, 2.85)</td>
<td>1.35 (0.54, 2.77)</td>
<td>1.85 (1.32, 2.54)</td>
</tr>
<tr>
<td>Herpes zoster (all)</td>
<td>3.82 (2.90, 4.94)</td>
<td>3.70 (2.19, 5.85)</td>
<td>3.79 (2.99, 4.74)</td>
</tr>
<tr>
<td>Malignancy (excluding NMSC)(^d)</td>
<td>0.82 (0.44, 1.40)(^e)</td>
<td>0.00 (0.00, 0.71)</td>
<td>0.62 (0.33, 1.06)(^f)</td>
</tr>
<tr>
<td>NMSC(^d)</td>
<td>0.77 (0.40, 1.34)(^e)</td>
<td>0.77 (0.21, 1.98)</td>
<td>0.77 (0.44, 1.25)(^f)</td>
</tr>
<tr>
<td>MACE(^d)</td>
<td>0.19 (0.04, 0.55)(^e)</td>
<td>0.58 (0.12, 1.69)</td>
<td>0.29 (0.10, 0.62)(^f)</td>
</tr>
<tr>
<td>Gastrointestinal perforation(^d,g)</td>
<td>0.13 (0.02, 0.46)(^e)</td>
<td>0.19 (0.00, 1.07)</td>
<td>0.14 (0.02, 0.42)(^f)</td>
</tr>
</tbody>
</table>

Data are reported as per the November 10 2017 data cut. \(^a\)All patients who received at least one dose of tofacitinib (5 or 10 mg BID) in Phase 2, OCTAVE Induction 1 and 2, OCTAVE Sustain or OCTAVE Open; \(^b\)Average daily dose tofacitinib dose of ≥15 mg; \(^c\)Average daily dose tofacitinib dose of <15 mg; \(^d\)Based on adjudication, excludes Phase 2; \(^e\)N=923; \(^f\)N=1124; \(^g\)Excludes preferred terms of pilonidal cyst, perirectal abscess, rectal abscess, anal abscess, perineal abscess and any preferred term containing the term fistula.

AE, adverse event; BID, twice daily; MACE, major adverse cardiovascular events; N, number of patients in the specified category; n, number of patients; NMSC, non-melanoma skin cancer; OLE, open-label, long-term extension; SAE, serious adverse event; UC, ulcerative colitis
Limitations

• The analysis presented here presents data derived from the ongoing Phase 3, multicentre, open-label, long-term extension study
• The efficacy analyses in OCTAVE Open are limited by sample size

Conclusions

• The majority of delayed responder patients with UC who achieved clinical response after extended induction with tofacitinib 10 mg BID demonstrated a durable response out to 3 years
• A substantial number of patients maintained clinical response, mucosal healing and remission up to 3 years, and effects were generally similar regardless of prior TNFi failure status
• The proportions of delayed responder patients with UC who achieved clinical response, mucosal healing and remission at Month 12 of open label treatment were similar to patients with UC who responded to the initial blinded 8 weeks of induction treatment
Acknowledgements

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Overview of the tofacitinib UC clinical programme

**Induction Cohort**
- **Phase 2 Induction** A3921063; NCT00787202
  - Tofacitinib 10 mg BID (N=48)
  - Placebo (N=48)
- **Phase 3 OCTAVE Induction 1a** A3921094; NCT01465763
  - Tofacitinib 10 mg BID (N=470)
  - Placebo (N=470)
- **Phase 3 OCTAVE Induction 2a** A3921095; NCT01458951
  - Tofacitinib 10 mg BID (N=429)
  - Placebo (N=429)

**Maintenance Cohort**
- **Phase 3 OCTAVE Sustain** A3921096; NCT01458574
  - Tofacitinib 10 mg BID (N=198)
  - Placebo (N=198)
  - Tofacitinib 5 mg BID (N=198)
  - Placebo (N=198)

**Overall Cohort**
- **Responders**
  - Completers
  - Non-responders and treatment failures
- **Non-responders**
  - Not in remission
  - Remission

**Notes**
- Final complete efficacy assessment at Week 8/52. Treatment continued up to Week 9/53
- Clinical response in OCTAVE Induction 1 and 2 was defined as a decrease from baseline total Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1
- Study A3921139 (OCTAVE Open) is ongoing
- Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0. In OCTAVE Open, 12 patients not in remission at OCTAVE Open entry received tofacitinib 5 mg BID and 1 patient in remission at OCTAVE Open entry received tofacitinib 10 mg BID, as protocol deviations
- BID, twice daily; N, number of patients treated in each treatment group; OLE, open-label, long-term extension; UC, ulcerative colitis