Tofacitinib for moderate to severe active ulcerative colitis

SUMMARY

Tofacitinib is intended for the treatment of moderate to severe active ulcerative colitis (UC) after the failure of conventional therapies. If licenced it would offer an additional treatment option for patients with moderate to severe UC, who do not respond to, are intolerant to, or are contraindicated for current drug therapies, including anti-TNF agents, a group who currently have few effective non-surgical therapies available. Tofacitinib is an oral Janus Kinase inhibitor that blocks signalling of several cytokines which may result in suppression of T and B cells whilst maintaining regulatory T-cell function.

It is estimated that there are currently 146,000 individuals in the UK with a diagnosis of UC. UC has an annual incidence in the UK of approximately 10 per 100,000. Active UC has a significant detrimental impact on a patient’s quality of life and work productivity. It is estimated that 90% of incident cases of UC are classified as mild or moderate. Approximately 30–40% of patients with UC will not respond to corticosteroid therapy, while 10-30% of UC patients receiving anti-TNF therapy experience primary non-response and 30-40% experience secondary non-response to treatment. In England, there were 156 deaths due to UC reported in 2012.

The aim of treatment for UC is to induce and maintain remission. Current therapies used to treat UC include: glucocorticoids, azathioprine, 6-mercaptopurine, 5-aminosalicylates, sulphasalazine, and TNF-alpha antagonists. Surgical intervention is also an option for patients with severe UC who develop serious complications. Although surgical intervention is considered curative, it is not the preferred treatment option as it may lead to a reduced quality of life. Tofacitinib is currently in four phase III clinical trials comparing its effect on inducing and maintaining remission against treatment with a placebo. These clinical trials are expected to complete between January 2015 and January 2017.
TARGET GROUP

- Ulcerative colitis (UC): active; moderate to severe – second line, after failure of conventional therapies.

TECHNOLOGY

DESCRIPTION

Tofacitinib (Xeljanz, CP-690550) is a novel oral Janus Kinase (JAK) inhibitor. It inhibits JAK1, 2 and 3 in vitro with functional specificity for JAK1 and 3 over 2. Inhibition of JAK1 and 3 blocks signalling of several cytokines, including IL-2, 4, 7, 9, 15 and 21 - these cytokines are integral to lymphocyte activation, function, and proliferation. Blockade of a common signalling molecule used by six important cytokines may result in suppression of both T and B cells while maintaining regulatory T-cell function. Tofacitinib is intended for use in patients with active moderate to severe UC who have had an inadequate response to, are intolerant to, or have contraindications for conventional UC therapies.

The dose of tofacitinib for this indication has yet to be determined - in phase III clinical trials; tofacitinib has been administered orally at 5mg and 10mg twice daily in induction studies and 5mg and 10mg twice daily in maintenance studies. Tofacitinib is currently in phase III clinical trials for rheumatoid arthritis, psoriasis, and psoriatic arthritis. It is phase II clinical trials for Crohn's disease, ankylosing spondylitis, psoriasis (topical application) and atopic dermatitis. Tofacitinib does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, tofacitinib will offer an additional treatment option for patients with moderate to severe UC, who do not respond to, are intolerant to, or are contraindicated for treatment with corticosteroids, thiopurine based drugs, and tumour necrosis factor (TNF)-alpha antagonists, a group of patients who currently have few effective non-surgical therapies available.

DEVELOPER

Pfizer Limited.

AVAILABILITY, LAUNCH OR MARKETING

Tofacitinib for ulcerative colitis is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

UC is a chronic inflammatory bowel disease (IBD) affecting the colonic mucosa, that can present at any age, but most commonly presents in patients under 25. The inflammation extends proximally from the rectum and involves the mucosa in a continuous fashion. Presenting symptoms include bloody diarrhoea, abdominal pain or discomfort, tenesmus and

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a Expert personal opinion.
urgency. Approximately 80% of patients with UC have a relapsing remitting course, characterized by intermittent flares interposed between variable periods of remission. Patients with UC have a higher risk of developing colorectal cancer than the general population. Active disease has a significant detrimental impact on a patient's quality of life and work productivity.

Patients with UC are classified on the basis of the clinical severity of the colonic inflammatory disease process along with the extent of disease. In children, the disease extends proximal to the splenic flexure in approximately 80% of cases, whereas in adult patients, the disease is more commonly limited to the left side of the colon. The disease has been defined as mild if there are less than four bowel motions per day and moderate if there are more than four bowel motions per day. Severe UC is defined as more than six bloody bowel motions per day with one or more signs of systemic toxicity (pulse more than 90 per minute, temperature more than 37.8°C, haemoglobin greater than 10.5g/dL, or erythrocyte sedimentation more than 30mm per hour).

This topic is relevant to:
- Improving quality of life for people with long term conditions (2013).

UC is the most common type of inflammatory bowel disease. It has an annual incidence in the UK of approximately 10 per 100,000 people annually, and a prevalence of approximately 240 per 100,000. This amounts to around 146,000 people in the UK with a diagnosis of UC. The peak incidence of UC is between the ages of 15 and 25 years, with a second, smaller peak in those aged between 55 and 65 years. In 2012, there were 42,243 admissions for UC (ICD-10 K51) in England, resulting in 76,360 bed-days and 50,680 finished consultant episodes. 156 deaths from UC were registered in England and Wales during 2012 (ICD-10 K51).

Approximately 90% of all incident cases of UC are mild or moderate in severity. An estimated 30–40% of patients with UC will not respond to corticosteroid therapy. Randomised controlled trials have shown that anti-TNFs initially fail in 10–30% of patients with inflammatory bowel diseases (primary failures), secondary non-response affects 30–40% of patients during the first year of anti-TNF therapy. The population likely to be eligible to receive tofacitinib could not be estimated from available published sources.

NHS or GOVERNMENT PRIORITY AREA

CLINICAL NEED and BURDEN OF DISEASE

RELEVANT GUIDANCE

NICE Guidance
- NICE technology appraisal in development. Ulcerative colitis (moderate to severely active) - vedolizumab [ID691]. Expected June 2015.

b Expert personal opinion.
CURRENT TREATMENT OPTIONS

The primary goal of treatment in UC is to induce and maintain remission. A number of therapeutic agents are commonly used to do so, including:

- Oral and topical (i.e. per rectum) corticosteroids for induction of remission.
- Oral and topical (i.e. per rectum) 5-aminosalicylates and sulphasalazine are used for induction and maintenance of remission.
- Purine analogues azathioprine and 6-mercaptopurine are used for maintenance of remission.
- Biological agents, particularly TNF-alpha antagonists, are used for the induction and maintenance of remission in steroid and immunosuppressant refractory disease.

Surgical intervention is advised in patients with: medically refractory disease, intolerance of drug adverse effects, development of colonic dysplasia or carcinoma and complications such as toxic megacolon. Although surgery is considered to be curative for patients with UC, the quality of life after restorative proctocolectomy is generally poorer than in patients who respond to medical therapy.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Octave Study, NCT01465763; tofacitinib vs. placebo; phase III.</th>
<th>Octave Study, NCT01458951; tofacitinib vs. placebo; phase III.</th>
<th>Octave Study, NCT014588574; tofacitinib vs. placebo; phase III extension.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of information</td>
<td>Trial registry</td>
<td>Trial registry</td>
<td>Trial registry</td>
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</table>

Other Guidance

<table>
<thead>
<tr>
<th>Location</th>
<th>EU (not UK), USA, Canada and other countries.</th>
<th>EU (incl UK), USA, Canada and other countries.</th>
<th>EU (not UK), USA, Canada and other countries.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>n=545 (planned); aged 18 years and older; diagnosed UC for at least 4 months; moderate to severe UC based on Mayo score criteria; failed or intolerant to at least one of the following: corticosteroids, azathioprine, 6 mercaptopurine (6 MP), or anti TNF-alpha therapy.</td>
<td>n=545 (planned); aged 18 years and older; diagnosed UC for at least 4 months; moderate to severe UC based on Mayo score criteria; failed or intolerant to at least one of the following: corticosteroids, azathioprine, 6MP, or anti TNF-alpha therapy.</td>
<td>n=654 (planned); aged 18 years and older; subjects who met inclusion criteria for NCT01465763 or NCT01458951 study, and who achieved clinical response in those studies.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to tofacitinib 10mg administered orally twice daily, or placebo, orally twice daily.</td>
<td>Randomised to tofacitinib 10mg administered orally twice daily, or placebo orally twice daily.</td>
<td>Randomised to placebo, tofacitinib 5mg, or tofacitinib 10mg all administered orally twice daily.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 8 weeks, follow-up 4 weeks.</td>
<td>Active treatment for 8 weeks, follow-up 4 weeks.</td>
<td>Active treatment for 52 weeks, follow-up 4 weeks.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Proportion of subjects in remission&lt;sup&gt;c&lt;/sup&gt; at week 8.</td>
<td>Proportion of subjects in remission&lt;sup&gt;d&lt;/sup&gt; at week 8.</td>
<td>Proportion of subjects in remission&lt;sup&gt;e&lt;/sup&gt; at week 52.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Mucosal healing&lt;sup&gt;e&lt;/sup&gt;, clinical response&lt;sup&gt;e&lt;/sup&gt;, clinical remission&lt;sup&gt;i&lt;/sup&gt;, symptomatic remission&lt;sup&gt;i&lt;/sup&gt;, deep remission&lt;sup&gt;k&lt;/sup&gt;, partial and total Mayo scores, quality of life&lt;sup&gt;i&lt;/sup&gt;.</td>
<td>Mucosal healing&lt;sup&gt;e&lt;/sup&gt;, clinical response&lt;sup&gt;e&lt;/sup&gt;, clinical remission&lt;sup&gt;i&lt;/sup&gt;, symptomatic remission&lt;sup&gt;i&lt;/sup&gt;, deep remission&lt;sup&gt;k&lt;/sup&gt;, partial and total Mayo scores, quality of life&lt;sup&gt;i&lt;/sup&gt;.</td>
<td>Mucosal healing&lt;sup&gt;e&lt;/sup&gt;, sustained steroid free remission among subjects in remission at baseline, quality of life&lt;sup&gt;k&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Primary completion date reported as January 2015.</td>
<td>Primary completion date reported as January 2015.</td>
<td>Primary completion date reported as January 2016.</td>
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</tbody>
</table>

<sup>c</sup> Remission defined as total Mayo score of 2 points or lower with no individual subscore exceeding 1 point and rectal bleeding subscore of 0.
<sup>d</sup> Mucosal healing defined as Mayo endoscopic subscore of 0 or 1.
<sup>e</sup> Decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1.
<sup>f</sup> Total Mayo score of 2 points or lower with no individual subscore exceeding 1 point.
<sup>g</sup> Total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point, and both rectal bleeding and stool frequency subscores of 0.
<sup>h</sup> Total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and both endoscopic and rectal bleeding subscores of 0.
<sup>i</sup> Measured by Inflammatory Bowel Disease Questionnaire, Euro Quality of Life Questionnaire (EQ-5D/VAS), Work Productivity and Activity Impairment-Ulcerative Colitis (WPAI-UC)- v2, Short Form -36, version 2, acute (SF-36v2 acute).
<sup>j</sup> Measured by Inflammatory Bowel Disease Questionnaire, EQ-5D/VAS, Patients’ Global Impression of Change (PGIC), Patient Reported Treatment Impact (PRTI), WPAI-UC- v2, SF-36v2 acute.
<sup>k</sup> Measured by Inflammatory Bowel Disease Questionnaire, EQ-5D/VAS, PRTI, WPAI-UC- v2, UC-Healthcare Resource Utilization (UC-HCRU), SF-36v2 acute.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Octave Study, NCT01470612; 5mg tofacitinib vs. 10mg tofacitinib; phase III extension.</th>
<th>NCT00787202; tofacitinib vs. placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Pfizer.</td>
<td>Pfizer.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
<td>Publication¹, trial registry².</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK), USA, Canada and other countries.</td>
<td>EU (incl UK) Brazil, Chile, Israel, Mexico and South Africa.</td>
</tr>
<tr>
<td>Design</td>
<td>Non-randomised.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=725 (planned); aged 18 years and older; subjects who completed induction studies NCT01465763 or NCT01458951 and classified as not meeting clinical response criteria, or subjects who completed maintenance study NCT01458574 or who discontinued treatment early in study NCT01458574 due to treatment failure.</td>
<td>n=195; aged 18 years and older; clinical diagnosis of UC ≥3 months prior to study entry; moderate to severe UC defined by Mayo score ≥6; endoscopic sub-score of ≥2 on Mayo score determined within 7 days of baseline.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Assigned to: tofacitinib 5mg or tofacitinib 10mg, both administered orally twice daily.</td>
<td>Randomised to: placebo, tofacitinib 0.5mg, tofacitinib 3mg, tofacitinib 10mg or tofacitinib 15mg, all administered orally twice daily.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 12 months, follow-up 4 weeks.</td>
<td>Active treatment for 8 weeks, follow-up 4 weeks.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Safety.</td>
<td>Clinical response.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Remission rates⁴, Mayo score remission rates⁵, mucosal healing⁶, quality of life⁷, infection, malignancy, cardiovascular events, proportion of subjects with addition of lipid lowering agents.</td>
<td>Clinical remission⁸, endoscopic response⁹, endoscopic remission⁸, partial Mayo Score, quality of life⁸, level of C-reactive protein (CRP).</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td>For placebo, 0.5mg, 3mg, 10mg, and 15mg groups respectively: clinical response, 42% (95% CI 28-56), 32% (95% CI 16-49), 48% (95% CI 31-66), 61% (95% CI 44-77), and 78% (95% CI 66-89); clinical remission, 10% (95% CI 2-19), 13% (95% CI 1-25), 33% (95% CI 17-49), 48% (95% CI 31-66), and 41% (95% CI 27-55).</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>-</td>
<td>Dose dependant increase in LDL and HDL cholesterol concentrations reported. AEs reported in ≥10% of participants: infection (in placebo, 0.5mg and 10mg arms).</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Primary completion date reported as December 2017.</td>
<td>September 2010.</td>
</tr>
</tbody>
</table>

¹ Measured by Inflammatory Bowel Disease Questionnaire.  
² Decrease from baseline flexible proctosigmoidoscopy subscore of the Mayo score at least 1 point.  
³ Findings of flexible proctosigmoidoscopy subscore of the Mayo score equals 0.
ESTIMATED COST and IMPACT

COST

The cost of tofacitinib is not yet known. The costs of other selected treatments for moderate to severe UC are summarised below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>5 mg/kg body weight intravenously (IV) on day 1, at 2 and 6 weeks after the first infusion, then every 8 weeks.</td>
<td>£14,267.08 (total cost for one year of treatment).</td>
</tr>
<tr>
<td>Adalimumab (monotherapy)</td>
<td>160mg initial dose, followed by 80mg in week 2 and 40mg every 2 weeks thereafter.</td>
<td>£10,573.2 (total cost for one year of treatment).</td>
</tr>
</tbody>
</table>

IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Other
- Reduced symptoms or disability
- No impact identified

Impact on Health and Social Care Services

- Increased use of existing services
- Re-organisation of existing services
- Other:
- Decreased use of existing services: oral treatment option compared to IV or injection administration of some current therapies.
- Need for new services
- None identified

Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Other increase in costs
- Other: uncertain unit cost compared to existing treatments.
- Reduced drug treatment costs
- Other reduction in costs: oral treatment option - reduced use of specialised services.
- None identified

Other Issues

- Clinical uncertainty or other research question identified
- None identified

REFERENCES


* Based on an average weight of 77.9kg, assumes wastage.
3 Garg SK, Croft AM, and Bager P. Helminth therapy (worms) for induction of remission in inflammatory bowel disease. The Cochrane Library 2014;1.
   Accessed 18 February 2014.
   Accessed 18 February 2014.
27 ClinicalTrials.gov. A study to investigate the safety and efficacy of CP-690,550 in patients with moderate and severe ulcerative colitis.
   http://www.clinicaltrials.gov/ct2/show/NCT00787202?term=nct00787202&rank=1
   Accessed 18 February 2014.