Tofacitinib for moderate to severe chronic plaque psoriasis – second line

SUMMARY

Tofacitinib is intended to be used as second line therapy for the treatment of moderate to severe plaque psoriasis in adult patients. If licensed, it would provide an alternative treatment option for this patient group. Tofacitinib is a novel oral janus kinase (JAK) inhibitor that inhibits JAK1,2 and 3 in vitro with functional specificity for JAK1 and 3. It is not currently licensed for any other indication.

Psoriasis is defined as a chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations. Plaque psoriasis is the most common type of psoriasis, representing 90% of cases. The estimated UK prevalence of psoriasis is 1.63%, 1.1% of people with psoriasis have severe disease. It has a bimodal onset, with the first peak occurring in persons aged 16 to 22 years, and the second in persons aged 57 to 60 years. Life expectancy in men and women with severe psoriasis is reduced by 3.5 and 4.4 years respectively. During 2010-11, there were 1,279 admissions for plaque psoriasis in England, resulting in 5,065 bed-days and 1,353 finished consultant episodes.

The clinical management of plaque psoriasis includes topical therapies, phototherapy, physical therapy and a range of pharmacological treatments including methotrexate, and TNF alpha inhibitors. Tofacitinib is in multiple phase III clinical trials comparing its effect on psoriasis area and severity index (PSAI) 75 response, and physician’s global assesment (PGA) response against placebo or etanercept. These trials are expected to complete between February 2013 and April 2017.
TARGET GROUP

- Plaque psoriasis: moderate to severe - adult patients who are candidates for systemic therapy; second line.

TECHNOLOGY

DESCRIPTION

Tofacitinib (tasocitinib, CP-690 500) is a novel oral janus kinase (JAK) inhibitor that inhibits JAK1,2 and 3 in vitro, with functional specificity for JAK1 and 3. Inhibition of JAK1 and 3 blocks signalling of several cytokines, including IL-2,4,7,9,15 and 21, which are required for lymphocyte activation, proliferation, and function, and therefore may result in modulation of the immune response. Tofacitinib is intended for the second line treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. It is administered orally at 5mg-10mg twice daily.

Tofacitinib is in phase III clinical trials for the treatment of moderate to severe ulcerative colitis and in phase II clinical trials for the treatment of transplant rejection and Crohn's disease.

INNOVATION and/or ADVANTAGES

If licensed, tofacitinib may provide an alternative treatment option for this patient group.

DEVELOPER

Pfizer Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Psoriasis is defined as a chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations. It is characterised by scaly skin lesions, which can be in the form of patches, papules, or plaques. The skin lesions of psoriasis are characterised by:

- Hyperproliferation of the epidermis.
- Dilation and proliferation of blood vessels in the dermis.
- Accumulation of inflammatory cells, particularly neutrophils and T-lymphocytes.

Chronic plaque psoriasis is typified by itchy, well demarcated circular-to-oval bright red/pink elevated lesions (plaques) with overlying white or silvery scale, distributed symmetrically over extensor body surfaces and the scalp.
NHS or GOVERNMENT PRIORITY AREA

No NHS or Government priority area was identified.

CLINICAL NEED and BURDEN OF DISEASE

Plaque psoriasis is the most common type of psoriasis, representing 90% of cases. The estimated UK prevalence of psoriasis is 1.63%\(^3\); 1.1% of people with psoriasis have severe disease\(^3\). It has a bimodal onset, with the first peak occurring in persons aged 16 to 22 years, and the second in persons aged 57 to 60 years. Females develop plaque psoriasis earlier than males, and patients with a positive family history for psoriasis also tend to have an earlier age of onset\(^4\). Acute flares or relapses of plaque psoriasis may evolve into more severe disease, such as pustular or erythrodermic psoriasis\(^4\). Up to 10-20% of patients with plaque psoriasis also experience psoriatic arthritis\(^4\).

Patients with psoriasis have a significantly reduced quality of life. Morbidity includes pruritus, dry and peeling skin, fissuring, self-consciousness and embarrassment about appearance, depression, inconvenience, and the adverse effects and high cost of anti-psoriatic treatment regimens\(^4\). Psoriasis is also associated with an increase in mortality\(^5\). Life expectancy in men and women with severe psoriasis is reduced by 3.5 and 4.4 years respectively\(^5\). The significant reduction in quality of life and psychosocial disability suffered by people with psoriasis underlies the need for prompt, effective treatment, and long-term disease control\(^6\). People with moderate to severe psoriasis may need second line therapies because of the extent and/or severity of the disease\(^6\); an estimated 7,086\(^a\) people in England will require such treatments\(^3\).

During 2011-12, there were 995 admissions for plaque psoriasis (ICD-10 L40.0) in England, resulting in 4,253 bed-days and 1,056 finished consultant episodes\(^7\).

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal. Adalimumab for the treatment of adults with psoriasis (TA146). June 2008\(^10\).
- NICE technology appraisal. Etanercept and efalizumab for the treatment of adults with psoriasis (TA103). July 2006\(^12\).
- NICE interventional procedure guidance. Grenz rays therapy for inflammatory skin conditions (IPG236). November 2007\(^14\).

\(^a\) Based on a population of 50,542,505.
Other Guidance

- SIGN. Diagnosis and management of psoriasis and psoriatic arthritis in adults. 2010\textsuperscript{5}.
- British Association of Dermatologists and Primary Care Dermatology Society. Clinical guideline: Recommendations for the initial management of psoriasis. 2009\textsuperscript{17}.
- British Association of Dermatologists' guidelines for biologic interventions for psoriasis. 2009\textsuperscript{18}.

EXISTING COMPARATORS and TREATMENTS

Current treatment options for plaque psoriasis include\textsuperscript{6,17,21,22}:

**Topical (alone or in combination)**

Emollients.
- Corticosteroids: betamethasone dipropionate.
- Vitamin D analogues: calcipotriol, calcitriol, tacalcitol and tazarotene (with or without phototherapy).
- Tars (with or without phototherapy).
- Dithranol (with or without phototherapy).
- Retinoids: tazarotene.
- Salicyclic acid.
- Tacrolimus ointment (not licensed for this indication).

**Phototherapy**
- Narrow band UVB and psoralen and UVA combination (PUVA).

**Systemic therapies (for the treatment of patients with severe or refractory psoriasis)**
- Oral retinoids: acitretin (with or without phototherapy).
- Hydroxycarbamide (not licensed for this indication).
- Fumaric acid esters: monoethylfumarate and dimethylfumarate (licensed in the EU but not in the UK).
- Drugs affecting the immune response: ciclosporin and methotrexate.

**Biologics (for the treatment of patients intolerant, contraindicated or refractory to other treatments)\textsuperscript{23}**
- Drugs affecting the immune response: adalimumab, etanercept, infliximab, and ustekinumab.
## EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01163253, A3921061; tofacitinib; phase III.</th>
<th>NCT01519089, A3921137; tofacitinib; phase III.</th>
<th>NCT01309737, A3921079, EUCTR2010-020003-73-DE; tofacitinib vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
<td>Japan.</td>
<td>EU, USA, Canada and other countries.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=3,200 (planned); 18 years and older; plaque psoriasis; previously participated in tofacitinib study.</td>
<td>n=88 (planned); 20 years and older; plaque psoriasis/psoriatic arthritis; moderate to severe covering at least 10% of body surface area; diagnosed for at least 12 months; PSAI score 12.</td>
<td>n=825 (planned); 18 years and older; plaque psoriasis; moderate to severe covering at least 10% of body surface area; diagnosed for at least 12 months; PSAI score 12.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Participants receive tofacitinib 10mg oral, twice daily for 3 months, followed by variable dosing with tofacitinib 5mg or 10mg oral, based on principle investigator (PI) discretion.</td>
<td>Randomised to tofacitinib 10mg or 5mg oral, twice daily for 16 weeks, followed by tofacitinib 10mg oral, twice daily for a further 4 weeks. Followed by variable dosing with tofacitinib 5mg or 10mg oral, based on PI discretion for 32 weeks.</td>
<td>Randomised to: Arm 1: tofacitinib 10mg oral, twice daily for 52 weeks. Arm 2: tofacitinib 5mg oral, twice daily for 52 weeks. Arm 3: placebo oral, twice daily for 16 weeks, followed by tofacitinib 10mg oral, twice daily for 36 weeks; or placebo oral, twice daily for 16 weeks, followed by tofacitinib 5mg oral, twice daily for 36 weeks.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for at least 2 years.</td>
<td>Active treatment for 52 weeks, follow-up 2-4 weeks.</td>
<td>Active treatment for 52 weeks.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Safety.</td>
<td>Safety; PGA response; PSAI 75 at week 16; ACRb 20 response.</td>
<td>PGA response; PASI 75 at week 16.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>PGAc response; PASI 50d, 75 and 90; change itch severity item (ISI) score; change in dermatology life quality index (DLQI); Euro-Qol 5 dimensions (EQ-5D).</td>
<td>PSAI 50, 75 and 90; DLQI score; work limitation questionnaire (WLQ) score; PGA response; nail psoriasis severity index (NAPSI); joint pain assessment (JPA) score; health assessment questionnaire disability index (HAQ-DI); ACR 50% and 70%.</td>
<td>PSAI 50; ISI score; DLQI score; change in NAPSI score; safety.</td>
</tr>
</tbody>
</table>

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b American College of Rheumatology (ACR). ACR 20 is a 20% improvement in tender or swollen joint counts.

c Physician’s Global Assessment (PGA) response. The proportion of subjects achieving PGA of ‘clear’ or ‘almost clear’.

d Loss of Psoriasis Area and Severity Index (PASI). PSAI 75 is a 75% reduction in PASI score.
<table>
<thead>
<tr>
<th>Expected reporting date</th>
<th>Primary completion date reported as Apr 2017.</th>
<th>Primary completion date reported as Mar 2014.</th>
<th>Primary completion date reported as Apr 2013.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>NCT01276639, A3921078, EUCCTR2010-019988-10-DE; tofacitinib vs placebo; phase III.</td>
<td>NCT01186744, A3921111, EUCCTR2010-020005-32-GB; tofacitinib vs placebo; phase III.</td>
<td>NCT01241591, A3921080; tofacitinib vs etanercept vs placebo; phase III.</td>
</tr>
<tr>
<td>Location</td>
<td>EU, USA, Canada and other countries.</td>
<td>EU (inc UK), USA, Canada, Brazil and Australia.</td>
<td>EU and other countries.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=825 (planned); 18 years and older; plaque psoriasis; moderate to severe, covering at least 10% of body surface area; diagnosed for at least 12 months; PASI score 12.</td>
<td>n=660; 18 years and older; plaque psoriasis; moderate to severe, covering at least 10% of body surface area; diagnosed for at least 12 months; PASI score, 12 or greater.</td>
<td>n=1,100; 18 years and older; plaque psoriasis; covering at least 10% of total body surface area.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to: Arm 1: tofacitinib 10mg oral, twice daily for 52 weeks. Arm 2: tofacitinib 5mg oral, twice daily for 52 weeks. Arm 3: placebo oral, twice daily for 16 weeks, followed by tofacitinib 10mg oral, twice daily for 36 weeks; or placebo oral, twice daily for 16 weeks, followed by tofacitinib 5mg oral, twice daily for 36 weeks.</td>
<td>Randomised to: Arm 1: tofacitinib 10mg oral, twice daily for 24 weeks, followed by placebo oral (treatment withdrawal), twice daily, for 4-16 weeks, followed by tofacitinib 10mg oral, twice daily for 16-28 weeks. Length of treatment is based on the PASI efficacy response. Arm 2: tofacitinib 10mg oral, twice daily for 56 weeks. Arm 3: tofacitinib 5mg oral, twice daily for 24 weeks, followed by placebo oral, twice daily for 4-16 weeks, followed by tofacitinib 5mg oral, twice daily for 16-28 weeks. Length of treatment is based on the PASI efficacy response. Arm 4: tofacitinib 5mg, oral, twice daily, for 56 weeks.</td>
<td>Randomised to: Arm 1: tofacitinib 5mg oral, twice daily in combination with subcutaneous (SC) placebo, twice weekly, both for 12 weeks. Arm 2: tofacitinib 10mg oral, twice daily in combination with SC placebo twice weekly, both for 12 weeks. Arm 3: placebo oral, twice daily in combination with etanercept 50mg SC twice weekly, both for 12 weeks. Arm 4: placebo oral, twice daily in combination with placebo SC twice weekly, both for 12 weeks.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 52 weeks.</td>
<td>Active treatment for 56 weeks.</td>
<td>Active treatment for 12 weeks.</td>
</tr>
</tbody>
</table>
Primary outcome/s | PGA response; PASI 75 response. | PASI 75 response; PGA response. | PASI 75 response; PGA response.  
Secondary outcome/s | Change in ISI score; DLQI; PASI 50 and 90; change in NAPSI score. | Change in ISI score; DLQI; safety. | PSAI 50 and 90; change ISI score; DLQI score; safety.  
Expected reporting date | Primary completion date reported as April 2013. | Primary completion date reported as Feb 2013. | Primary completion date reported as Jan 2013.  

Trial | NCT00678210, A3921047; tofacitinib vs placebo; phase II.  
Sponsor | Pfizer.  
Status | Complete and published.  
Source of information | Trial registry and publication.  
Location | USA and Canada.  
Design | Randomised, placebo-controlled.  
Participants | n=197; aged 18 years and older; diagnosed with plaque psoriasis for at least 6 months; covering at least 15% of total body area.  
Schedule | Randomised to tofacitinib 2mg, 5mg, 15mg, or placebo oral, twice daily for 12 weeks.  
Follow-up | Active treatment 12 weeks, follow-up 4 weeks.  
Primary outcome/s | PSAI 75.  
Secondary outcome/s | PSAI 50 and 90 response; PGA response.  
Key results | For tofacitinib 2mg, 5mg, 15mg, and placebo respectively: PASI 75 response, 25.0% (90% CI, 12.2-33.8), 40.8% (90% CI, 26.8-50.8), 66.7% (90% CI, 53.0-76.3), 20.0%; PGA response, 24.5%, 40.8%, 72.9%, 10.0%.  
Adverse effects (AEs) | Common AEs include: diarrhoea, 2.0%; nasopharyngitis, 5.6%; sinusitis, 3.0%; upper respiratory tract infection, 7.6%; back pain, 3.0%; headache, 5.1%; psoriasis, 3.0%.  

ESTIMATED COST and IMPACT

COST

The cost of tofacitinib is not yet known. The costs of other treatments for plaque psoriasis are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit Cost</th>
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</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>80mg SC; then 40mg SC on alternate weeks one week after initial dose.</td>
<td>£352 (40mg, prefilled syringe)</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>25mg SC twice weekly or 50mg SC once weekly.</td>
<td>£89 (25mg, prefilled syringe)</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>5mg/kg IV repeated at 2 and 6 weeks; then every 8 weeks.</td>
<td>£420 (100mg vial)</td>
</tr>
<tr>
<td>Ustekinumab (Stelara)</td>
<td>Initially 45mg, then 45mg 4 weeks after initial dose, then 45mg every 12 weeks.</td>
<td>£2147.00 (45mg, prefilled syringe)</td>
</tr>
</tbody>
</table>

* Based on an average body weight of 76.9kg.
**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other:
  - No impact identified

**Impact on Services**
- Increased use of existing services
  - Decreased use of existing services
- Re-organisation of existing services
  - Need for new services
- Other:
  - None identified

**Impact on Costs**
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
  - Other reduction in costs:
- Other: uncertain unit cost compared to alternative treatment options.
  - None identified

**Other Issues**
- Clinical uncertainty or other research question identified: *Expert opinion suggests data on tofacitinib vs methotrexate would be helpful.*
  - None identified

**REFERENCES**

