Tildrakizumab for moderate to severe plaque psoriasis

SUMMARY

Tildrakizumab is intended for use in patients with moderate to severe plaque psoriasis who have failed to respond to, have contraindications to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA (psoralen ultraviolet light) therapy. If licensed, it will offer an additional treatment option for these patients who have not responded to topical or systemic therapies, and offer an alternative to other biological agents. Tildrakizumab is a high affinity humanised IgG1/k monoclonal antibody. It specifically targets the interleukin-23 (IL-23) p19 subunit, a receptor which plays an important role in the pathogenesis of autoimmune inflammation, by stimulating the production of Th17 cells, which in turn produce pro-inflammatory molecules. Tildrakizumab does not currently have Marketing Authorisation in the EU for any indication.

The prevalence of psoriasis in England is estimated to be around 1.63%, equating to approximately 900,000 people with the condition. Plaque psoriasis accounts for around 90% of cases and approximately 20% have moderate to severe psoriasis (15% moderate, 5% severe). The estimated prevalence of people currently eligible for biological therapy in England is 3% of those with psoriasis, equating to around 27,000 people. However, because of the nature of the condition, not all patients eligible for biologic treatments will currently be identified and treated with them. In 2013-14, there were 1,454 hospital admissions in England as a result of psoriasis vulgaris equating to 1,537 finished consultant episodes and 3,912 bed days. Thirty deaths from psoriasis were registered in England and Wales during 2013.

Treatment options for psoriasis aim to reduce symptoms and improve patient quality of life. Topical treatments are usually offered as first line therapy, followed by phototherapy and/or systemic therapies as second line treatment, and biological therapies as third line treatment regimes. Tildrakizumab is in three phase III clinical trials comparing its effect on Psoriasis Area Severity Index (PASI) against treatment with etanercept or placebo. These trials are expected to be completed by 2019.
TARGET GROUP

- Plaque psoriasis: moderate to severe – patients who have failed to respond to, have a contraindication to, or are intolerant to other systemic therapies.

TECHNOLOGY

DESCRIPTION

Tildrakizumab (SCH-900222; MK-3222; anti-IL-23 MAb) is a high affinity humanised IgG1/k monoclonal antibody. It specifically targets the interleukin-23 (IL-23) p19 subunit, a receptor which plays an important role in the pathogenesis of autoimmune inflammation, by stimulating the production of Th17 cells, which in turn produce pro-inflammatory molecules. Tildrakizumab is intended for use in patients with moderate to severe plaque psoriasis who have failed to respond to, have contraindications to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA (psoralen ultraviolet light) therapy. Tildrakizumab is administered subcutaneously (SC); in the phase III clinical trials, a dose of either 200mg or 100mg was administered at weeks 0, 4, 16 and 28.

Tildrakizumab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, tildrakizumab will offer an additional treatment option for patients with plaque psoriasis who have not responded to topical or systemic therapies, and will offer an alternative to other biological agents.

DEVELOPER

Merck Sharp & Dohme Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Psoriasis is an inflammatory skin condition characterised by well-defined, sharply demarcated, erythematous plaques, which can be one centimetre to several centimetres in size. Plaques may form across specific areas such as the scalp, trunk, limbs, buttocks, elbows and knees, but can also manifest across the entire body causing pain and pruritus. Plaques appear as dry, thin, silvery-white scales, and often smaller plaques merge forming larger plaques, particularly over the leg and trunk. The cause of psoriasis is not known although genetics, the environment, and an overactive immune system (in particular T cells) are thought to play a part. Psoriasis typically follows a relapsing and remitting course, with flare ups occurring spontaneously. Contributors to flare ups include stress, infections, medications, sunlight, trauma, hormonal changes, smoking and alcohol.
Patients with psoriasis often experience feelings of self-consciousness and embarrassment, and as a result, may suffer unemployment, social isolation, and depression; all factors which contribute to a reduction in overall patient quality of life. The adverse psychosocial issues associated with the condition also contribute to worsening outcomes for patients with psoriasis.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

The prevalence of psoriasis in England is estimated to be around 1.63%, equating to approximately 900,000 people with the condition. Plaque psoriasis accounts for around 90% of cases and approximately 20% have moderate to severe disease (15% moderate, 5% severe). Onset may occur at any age, although it is uncommon in children (prevalence 0.71%), with the majority of cases occurring before the age of 35. Life expectancy in men and women with severe psoriasis is reduced by 3.5 and 4.4 years respectively, primarily due to metabolic syndrome and heart disease. Females typically develop plaque psoriasis earlier than males, and patients with a positive family history for psoriasis also tend to have an earlier age of onset. Acute flares or relapses of plaque psoriasis may evolve into more severe disease, such as pustular or erythrodermic psoriasis.

The estimated prevalence of people currently eligible for biological therapy in England is 3% of those with psoriasis, equating to around 27,000 people. However, because of the nature of the condition, not all patients eligible for biologic treatments will currently be identified and/or treated with these agents.

In 2013-14, there were 1,454 hospital admissions in England as a result of psoriasis vulgaris (ICD-10 L40.0), equating to 1,537 finished consultant episodes and 3,912 bed days. Thirty deaths from psoriasis were registered in England and Wales during 2013 (ICD-10 L40).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Psoriasis (plaque, moderate to severe) - apremilast [ID679]. Expected August 2015.

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*a Based on Office for National Statistics mid-2013 population estimate for England.*

Other Guidance

• Scottish Intercollegiate Guidelines Network. Diagnosis and management of psoriasis and psoriatic arthritis in adults (121). 2010.
• British Association of Dermatologists and Primary Care Dermatology Society. Clinical guideline: Recommendations for the initial management of psoriasis. 2009.

CURRENT TREATMENT OPTIONS

Treatment options for psoriasis aim to reduce symptoms and improve patient quality of life. Topical treatments are usually offered as first line therapy, followed by phototherapy and/or systemic therapies as second line treatment, and biological therapies as third line treatment regimes. The majority of psoriasis cases are managed at the primary care level, though up to 60% of patients may require referral to a specialist.

Current treatment options for plaque psoriasis include:

Topical (alone or in combination)
• Emollients.
• Corticosteroids: betamethasone dipropionate.
• Vitamin D analogues: calcipotriol, calcitriol, tacalcitol (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
• Broad- or narrow-band UVB and psoralen and UVA combination (PUVA).

Systemic conventional disease modifying therapies (for the treatment of patients with moderate to severe or refractory psoriasis)
• Oral retinoids: acitretin (with or without phototherapy).
• Hydroxychloroquine (not licensed for this indication).
• Ciclosporin.
• Methotrexate.
- Fumaric acid esters: Fumaderm (not licensed in the UK for this indication)\(^b\).
- Apremilast.

**Biological therapies (for the treatment of patients with moderate to severe psoriasis who are candidates for systemic therapies)**
- Secukinumab (IL-17A inhibitor).

**Biological therapies (for the treatment of patients intolerant, contraindicated or refractory to other systemic conventional disease modifying treatments and/or phototherapy)**
- Adalimumab (TNF-α inhibitor).
- Etanercept (TNF-α inhibitor).
- Infliximab (TNF-α inhibitor).
- Ustekinumab (IL-12 and IL-23 inhibitor).

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
<th>Schedule</th>
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<tbody>
<tr>
<td>NCT01936688, MK-3222-012, 2013-001740-54; tildrakizumab vs etanercept vs placebo; phase III.</td>
<td>Merck Sharp &amp; Dohme Corp.</td>
<td>Ongoing.</td>
<td>Trial registry(^1).</td>
<td>Not reported.</td>
<td>Randomised, active- and placebo-controlled.</td>
<td>n=1,050 (planned); aged 18 years and older; moderate to severe plaque psoriasis; candidate for phototherapy or systemic therapy. Inclusion criteria for extension studies: must have completed part 2 and achieved at least Psoriasis Area Severity Index (PASI)(^c) 50 response by the end of part 2.</td>
<td></td>
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<tr>
<td>NCT01729754, MK-3222-011, P07771; tildrakizumab vs etanercept vs placebo; phase III extension.</td>
<td>Merck Sharp &amp; Dohme Corp.</td>
<td>Ongoing.</td>
<td>Trial registry(^20).</td>
<td>Not reported.</td>
<td>Randomised, active-controlled.</td>
<td>n=1,050 (planned); aged 18 years and older; moderate to severe plaque psoriasis; candidate for phototherapy or systemic therapy; must have completed part 3 of previous NCT01722331 study and achieved at least PASI 50 response by the end of part 3.</td>
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<tr>
<td>NCT01722331, MK-3222-010, 2012-002255-42, P07770; tildrakizumab vs placebo; phase III extension.</td>
<td>Merck Sharp &amp; Dohme Corp.</td>
<td>Ongoing.</td>
<td>Trial registry(^21).</td>
<td>Not reported.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=885 (planned); aged 18 years and older; moderate to severe plaque psoriasis; candidate for phototherapy or systemic therapy. Inclusion criteria for extension studies: must have completed part 3 and achieved at least a PASI 50 response by the end of part 3; received active tildrakizumab treatment within 12 weeks prior to the end of part 3.</td>
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</table>

\(^b\) Expert personal communication.

\(^c\) PASI is an index used to express the severity of psoriasis. It combines the severity (erythema, induration and desquamation) and percentage of body surface area.
week 12, and then once weekly through to week 28.

Arm 1: participants with a PASI 75 response at week 28 will be re-randomised to either continue tildrakizumab 200mg or 100mg SC at weeks 28, 40 and 52; PASI 50 response but <PASI 75 response will continue to receive tildrakizumab every 12 weeks; no PASI 50 response will be discontinued from the study.

Arm 2: participants with PASI 75 response at week 28 will continue to receive tildrakizumab 100mg every 12 weeks; PASI 50 response but <PASI 75 response will be re-randomised to receive tildrakizumab 100mg or 200mg SC every 12 weeks. <PASI 50 response will be discontinued from the study.

Arm 3: participants will continue to receive treatment every 12 weeks.

Eligible participants that choose to enrol in the extension study will have an additional treatment period of up to 192 weeks and will be followed for an additional 20 weeks in each follow-up period. Each participant will receive tildrakizumab 200mg or 100mg SC every 12 weeks for up to study week 220 according to their treatment assignment at the end of part 2.
according to their re-randomised treatment assignment. 

**Arm 4:** >PASI 75 response at week 28 will be discontinued from the study; <PASI 75 response at week 28 will be crossed over to tildrakizumab 200mg SC at week 32, 36 and 28.

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Active treatment period 28 weeks, follow-up 20 weeks.</th>
<th>Active treatment period 52 weeks, follow-up 20 weeks.</th>
<th>Active treatment period 12 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome/s</td>
<td>PASI 75 at week 12, Physician's Global Assessment (PGA).</td>
<td>PASI 75 at week 12, PGA score, safety.</td>
<td>PASI 75 at week 12, PGA score, safety.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>PASI 90 at week 12 and 28, Dermatology Life Quality Index (DLQI), DLQI score of 0 or 1 at week 12, Nail Psoriasis Severity Index (NAPSI) at week 12.</td>
<td>PASI 75 at week 28, PGA score at week 28, PASI 90 at week 12 and 28, PASI 100 score at week 12 and 28, DLQI at week 12 and 28, DLQI of 0 or 1 at week 12 and 28, NAPSI at week 12.</td>
<td>PASI 90, PASI 100, DLQI, DLQI score of 0 or 1 at week 12.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as Aug 2018.</td>
<td>Study completion date reported as Oct 2019.</td>
<td>Study completion date reported as Aug 2019.</td>
</tr>
</tbody>
</table>

**Trial**

NCT01225731, P05495, 2009-017272-24, MK-3222-003; tildrakizumab vs placebo; phase II.

**Sponsor**

Merck Sharp & Dohme Corp.

**Status**

Complete and published in abstract.

**Source of information**

Abstract 22, trial registry 23.

**Location**

EU (inc UK), USA, Canada and other countries.

**Design**

Randomised, placebo-controlled.

**Participants**

n=339; aged 18 years and older; moderate to severe chronic plaque psoriasis defined by disease affecting ≥10% body surface area; moderate or greater score on PGA; PASI score ≥12 at baseline; diagnosis of predominantly plaque psoriasis for ≥6 months; candidate for phototherapy or systemic therapy.

**Schedule**

Patients were randomised to 5 groups. In part 1 of the study, all patients in each group received the specified dose of treatment or placebo at week 0 and week 4. In part 2, patients within each group were divided into responders (R) and non-responders (NR) and received a specified SC dose of tildrakizumab at week 16 then once every 12 weeks. 

**Part 1**

- Group 1, tildrakizumab 5mg SC; group 2, tildrakizumab 25mg SC; group 3, tildrakizumab 100mg SC; group 4, tildrakizumab 200mg SC; group 5, placebo SC.

**Part 2**

- Group 1, R: tildrakizumab 5mg SC, NR: tildrakizumab 100mg SC; group 2 R: tildrakizumab 25mg SC, NR: tildrakizumab 100mg SC; group 3, R: tildrakizumab 100mg or 25mg SC, NR: tildrakizumab 200mg SC; group 4, R: tildrakizumab 200mg or 100mg SC, NR: tildrakizumab 200mg SC; group 5, R: tildrakizumab 25mg SC, NR: tildrakizumab 100mg SC.

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* The PGA measures the physician’s impression of the disease (psoriasis).
Follow-up | Active treatment period 52 weeks, follow-up until week 72.
---|---
Primary outcome/s | ≥75% improvement in PASI 75 at week 16.
Secondary outcome/s | ≥75% improvement in PASI 75 at week 12; PGA of cleared or minimal at week 16.
Key results | No significant difference was observed in PASI 75 at week 52 following dose reduction from 200mg to 100mg vs. remaining on 200mg at week 16. There was a significant loss of PASI 75 (p=0.005) and PGA (p=0.02) response at week 52 following dose reduction from 100mg to 25mg vs. remaining on 100mg. PASI 75 and PGA responders at week 52 generally maintained response following study drug discontinuation; PASI 75 responses for the 100mg to 100mg group (part 1 to part 2 dose) was 97% and 96% at weeks 52 and 72, respectively, 70% and 62% for 100mg to 25mg group, 97% and 89% for 200mg to 200mg group and 91% and 70% for 200mg to 100mg group. Median time to relapse (i.e., >50% reduction of week 52 improvement from baseline) in subjects receiving 100mg was 21.5 weeks. Less than 50% of subjects receiving 200mg had >50% reduction in PASI score by week 72.
Adverse effects (AEs) | Serious AEs that were possibly related to tildrakizumab included bacterial arthritis and lymphoedema, melanoma, stroke, epiglottis and knee infection.

**ESTIMATED COST and IMPACT**

**COST**

The cost of tildrakizumab is not yet known. The costs of other selected biological therapies for psoriasis are detailed below44.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit cost</th>
<th>Annual cost</th>
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<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>Initially 80mg SC, then 40mg on alternate weeks, one week after initial dose.</td>
<td>£357.50 (40mg, prefilled syringe).</td>
<td>£9,295.</td>
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<tr>
<td>Etanercept (Enbrel)</td>
<td>25mg SC twice weekly or 50mg once weekly.</td>
<td>£89.38 (25mg, prefilled syringe).</td>
<td>£9,295.</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>5mg/kg intravenously repeated 2 weeks and 6 weeks after initial dose and then every 8 weeks.</td>
<td>£419.62 (100mg, vial).</td>
<td>£10,910†.</td>
</tr>
<tr>
<td>Ustekinumab (Stelara)</td>
<td>Initially 45mg SC, then 45mg 4 weeks after initial dose, then 45mg every 12 weeks.</td>
<td>£2,147 (45mg, prefilled syringe).</td>
<td>£12,882.</td>
</tr>
</tbody>
</table>

**IMPACT - SPECULATIVE**

Impact on Patients and Carers
- ✗ Reduced mortality/increased length of survival
- ✓ Reduced symptoms or disability
- ✓ Other: Impact on quality of life of families/carers and patients, including social wellbeing and education
- ✗ No impact identified

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4 Based on an average weight of 77.3kg. Assumes wastage.

† Following loading doses and based on an average 6.5 doses per year.
Impact on Health and Social Care Services

- Increased use of existing services
- Re-organisation of existing services
- Other: None identified

- Decreased use of existing services
- 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:
  - None identified

Other Issues

- Clinical uncertainty or other research question identified: expert opinion suggests that in terms of performance it would be important to establish efficacy of tildrakizumab vs the more commonly used biologics – adalimumab and ustekinumab.

  *It is suggested that 10% of patients with psoriasis also have a psoriatic arthropathy, an important future research question, therefore, would be the efficacy in treating joint disease.*

REFERENCES


*Expert personal communication.*


22 Langley RGB, Thaci D, Papp KA et al. MK-3222, an anti-IL-23p19 humanized monoclonal antibody, provides significant improvement in psoriasis over 52 weeks of treatment that is maintained after discontinuation of dosing. Journal of the American Academy of Dermatology 2014;5(70):supplement 1, AB176.
