Ixekizumab is intended for the treatment of moderate to severe chronic plaque psoriasis in adults who are candidates for systemic therapy. If licensed, ixekizumab will offer an additional treatment option for this patient group. Treatment with ixekizumab may result in some patients achieving near/full clearance of psoriasis symptoms. Ixekizumab is a humanised immunoglobulin G subclass 4 (IgG4) monoclonal antibody that neutralises interleukin-17A (IL-17), which is a key T cell-derived cytokine involved in inducing and mediating inflammation. It 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 around 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/or treated with these agents. 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. Ixekizumab is currently in three phase III clinical trials comparing its effect on the Psoriasis Area Severity Index (PASI) against treatment with etanercept and placebo. These trials are expected to be completed by 2019.
TARGET GROUP

- Plaque psoriasis: moderate to severe; chronic – adults who are candidates for systemic therapies.

TECHNOLOGY

DESCRIPTION

Ixezizumab (LY2439821, anti-IL-17 monoclonal antibody) is a humanised immunoglobulin G subclass 4 (IgG4) monoclonal antibody that neutralises interleukin-17A (IL-17), which is a key T cell-derived cytokine involved in inducing and mediating inflammation. Ixezizumab is intended for the treatment of moderate to severe chronic plaque psoriasis in adults who are candidates for systemic therapy. It is administered subcutaneously (SC) at a frequency and dose to be determined from the company’s phase III trial. The company anticipate that the dosing regimen will consist of a 160mg initial dose, followed by 80mg dosing through the induction and maintenance periods.

Ixezizumab does not currently have Marketing Authorisation in the EU for any indication. Ixezizumab is also in phase III clinical trials for psoriatic arthritis; and phase II for rheumatoid arthritis.

INNOVATION and/or ADVANTAGES

If licensed, ixezizumab will offer an additional treatment option for patients with moderate to severe plaque psoriasis who are candidates for systemic therapy. Treatment with ixezizumab may result in some patients achieving near/full clearance of psoriasis symptoms.

DEVELOPER

Eli Lilly and Company Limited.

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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*Based on Office for National Statistics mid-2013 population estimate for England.*
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: e.g. betamethasone dipropionate.
- Vitamin D analogues: calcipotriol, calcitriol, tacalcitol (with or without phototherapy).
- Tars (with or without phototherapy).
- Dithranol (with or without phototherapy).
- Retinoids: tazarotene.
- Salicylic 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).
- Hydroxyxycarbamide (not licensed for this indication).
- Ciclosporin.
- Methotrexate.
Apremilast.

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

Biological therapies (for the treatment of patients intolerant, contraindicated or refractory to other systemic conventional disease modifying treatments and/or phototherapy)
- Secukinumab (IL-17A inhibitor).
- 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>UNCOVER-1, NCT01474512, 12972, IIIF-MC-RHAZ; ixekizumab vs placebo; phase III.</th>
<th>UNCOVER-2, NCT01597245, 12973, IIIF-MC-RHBA; ixekizumab vs etanercept vs placebo; phase III.</th>
<th>UNCOVER-3, NCT01646177, 13685, IIIF-MC-RHBC; ixekizumab vs etanercept vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<td>EU, USA, Canada and other countries.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=1,296; aged 18 years and older; plaque psoriasis (at least 10% of body surface area); chronic; moderate to severe; sPGA³ score of at least 3 and PASI² score of at least 12 at screening and at first dose of study drug; candidate for phototherapy and/or systemic therapy.</td>
<td>n=1,224; aged 18 years and older; plaque psoriasis (at least 10% of body surface area); chronic; moderate to severe; sPGA³ score of at least 3 and PASI² score of at least 12 at screening and at first dose of study drug; candidate for phototherapy and/or systemic therapy.</td>
<td>n=1,346; aged 18 years and older; plaque psoriasis (at least 10% of body surface area); chronic; sPGA score of at least 3 and PASI score of at least 12 at screening and at randomisation; candidate for phototherapy and/or systemic therapy.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Induction period (up to week 12):</td>
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</tr>
<tr>
<td></td>
<td>Randomised to: Arm 1: ixekizumab 160mg SC injection at week 0, then ixekizumab 80mg once every two weeks for 12 weeks. At week 12, responders (sPGA 0 or 1) to treatment are re-randomised to</td>
<td>Randomised to: Arm 1: ixekizumab 160mg SC injection at week 0, then ixekizumab 80mg once every two weeks for 12 weeks. At week 12, responders to treatment are re-randomised to</td>
<td>Randomised to: Arm 1: ixekizumab 160mg SC injection at week 0, then ixekizumab 80mg once every two weeks for 12 weeks. At week 12, patients are assigned to dosing regimen 2.</td>
</tr>
</tbody>
</table>

¹ The static PGA (sPGA) measures the physician’s impression of the disease (psoriasis).
² PASI (Psoriasis Area Severity Index) is an index used to express the severity of psoriasis. It combines severity (erythema, induration and desquamation) and percentage of affected body surface area.
randomised to placebo, dosing regimen 2 or dosing regimen 3.  
Arm 2: ixekizumab 160mg SC injection at week 0, then ixekizumab 80mg once every four weeks for 12 weeks. At week 12, responders to treatment are re-randomised to placebo, dosing regimen 2 or dosing regimen 3.  
Placebo: placebo SC injection at week 0, then once every two weeks for 12 weeks. At week 12, placebo non-responders receive starting dose of ixekizumab 160mg SC, followed by ixekizumab 80mg SC every 4 weeks for 48 weeks. Placebo responders remain on placebo SC every 4 weeks until relapse whereupon patients are placed on ixekizumab 80mg SC every 4 weeks.  
**Maintenance dosing period:**  
Randomised to:  
Placebo: placebo SC every 4 weeks for 48 weeks.  
Dosing regimen 2: ixekizumab 80mg SC every 4 weeks for 48 weeks.  
Dosing regimen 3: ixekizumab 80mg SC every 12 weeks for 48 weeks.  
Non-responders (sPGA >1) at week 12 and patients who relapsed (sPGA ≥3) were placed on ixekizumab 80mg SC every 4 weeks.  

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Induction plus maintenance treatment period up to 60 weeks.</th>
<th>Induction plus maintenance treatment period up to 60 weeks.</th>
<th>Active treatment period 264 weeks.</th>
</tr>
</thead>
</table>

**Arm 2:** ixekizumab 160mg SC at week 0, then ixekizumab 80mg once every four weeks. At week 12 patients are assigned to dosing regimen 2.  
Arm 3: etanercept 50mg SC twice weekly for 12 weeks. At week 12, patients are assigned to dosing regimen 2.  
Placebo: placebo for ixekizumab SC at week 0, then once every two weeks for 12 weeks. Placebo for etanercept SC twice weekly for 12 weeks. At week 12, patients are assigned to dosing regimen 2.  

**Long term extension period from week 12 up to week 264.**  

**Dosing regimen 2:** ixekizumab 80mg every 4 weeks.  

**Arm 2:** ixekizumab 160mg SC at week 0, then ixekizumab 80mg once every four weeks. At week 12 patients are assigned to dosing regimen 2.  
Arm 3: etanercept 50mg SC twice weekly for 12 weeks. At week 12, patients are assigned to dosing regimen 2.  
Placebo: placebo for ixekizumab SC at week 0, then once every two weeks for 12 weeks. Placebo for etanercept SC twice weekly for 12 weeks. At week 12, patients are assigned to dosing regimen 2.  

**Long term extension period from week 12 up to week 264.**  

**Dosing regimen 2:** ixekizumab 80mg every 4 weeks.
NIHR Horizon Scanning Centre

<table>
<thead>
<tr>
<th>Primary outcome/s</th>
<th>Long-term extension period up to 264 weeks.</th>
<th>Long-term extension period up to 264 weeks.</th>
<th>Long-term extension period up to 264 weeks.</th>
</tr>
</thead>
</table>

**Key results**
For patients treated with ixekizumab either every four weeks or every two weeks, 78-90% achieved at least a 75% reduction in PASI score (PASI 75) at 12 weeks. Additionally, 31-41% of these patients achieved PASI 100, or clear skin, at week 12. For comparison 5-7% of patients treated with etanercept in the NCT01597245 and NCT01646177 studies achieved PASI 100.

**Adverse effects (AEs)**
The most frequently reported AEs (more than 5% across all three studies) were nasopharyngitis and injection site reaction. Most injection site reactions were mild, and most patients who experienced an injection site reaction continued treatment with ixekizumab.

**Expected reporting date**
- Study completion date reported as Apr 2018.
- Study completion date reported as Dec 2018.
- Study completion date reported as Feb 2019.

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**Trial**
NCT01107457, 12060, I1F-MC-RHAJ; ixekizumab vs placebo; phase II.

**Sponsor**
Eli Lilly and Company.

**Status**
Ongoing and published.

**Source of information**
Trial registry<sup>23</sup>, publication<sup>24</sup>.

**Location**
USA and Denmark.

**Design**
Randomised, placebo-controlled.

**Participants**
n=142; aged 18 years and older; plaque psoriasis (at least 10% of body surface area); chronic; moderate to severe; sPGA score of at least 3 at screening and at randomisation; candidate for systemic therapy. Participants must have completed treatment period part A before starting part B.

**Schedule**
Part A
- Randomised to ixekizumab 10mg, 25mg, 75mg, 150mg or placebo SC on weeks 0, 2, 4, 8, 12 and 16.

Part B
- Participants receive ixekizumab 80mg SC every 4 weeks until week 236.

**Follow-up**
Active treatment period up to 264 weeks.

**Primary outcome/s**
PASI 75.

**Secondary outcome/s**
- sPGA score up to 240 weeks, AEs, Hospital Anxiety and Depression Scale (HADS), 16-item Quick Inventory of Depressive Symptoms-Self Rated (QIDS-SR16), Patient global assessment (PatGA), pain Visual Analog Scale (VAS), Medical Outcomes Study Sleep Scale (MOS-S), Psoriasis Medical Care Resource Utilization (PMRU), Work Productivity and Activity Impairment Questionnaire (WPAIQ), medical outcomes study Short Form-36 (SF-36), Nail Psoriasis Severity Index (NAPSI) in participants with nail psoriasis, Scalp Psoriasis Severity Index (SPSI) in participants with scalp psoriasis, Palmoplantar Psoriasis Severity Index (PPSI) in participants with palmoplantar psoriasis, PASI score at week 240, Dermatology Life Quality Index (DLQI), PASI-75 at week 32, sPGA score of 0-1 with at least a 2 point improvement at week 32.

**Key results**
For ixekizumab 10mg, 25mg, 75mg, 150mg vs placebo respectively (± standard deviation, p values vs placebo):
PASI score, 10.2±10.0 (p<0.001), 4.5±6.2 (p<0.001), 2.5±3.7 (p<0.001), 2.4±4.2

<sup>23</sup> Measured through patient reported outcomes.
Adverse effects (AEs) | The most common adverse events were nasopharyngitis, upper respiratory infection, injection site reaction, and headache.
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Expected reporting date | Study completion date reported as Jul 2016.

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**ESTIMATED COST and IMPACT**

**COST**

The cost of ixekizumab is not yet known. The costs of other selected biological therapies for psoriasis are detailed below.\(^{25,26}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit cost</th>
<th>Annual cost</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>25mg SC twice weekly or 50mg once weekly.</td>
<td>£89.36 (25mg, prefilled syringe).</td>
<td>£9,295.</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>5mg/kg IV repeated 2 weeks and 6 weeks after initial dose and then every 8 weeks.</td>
<td>£419.62 (100mg, vial).</td>
<td>£10,910 (following loading doses and based on average 6.5 doses per year).</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

**Impact on Health and Social Care 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 and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
  - Other: uncertain unit cost compared to existing treatments, expert opinion suggests that indirect costs such as return to employment are also an important factor to consider.
- None identified
- Other reduction in costs:
- None identified

Other Issues

- Clinical uncertainty or other research question identified: expert opinion implies that an important question to consider with these biological therapies is whether there are biomarkers (co-diagnostics) that can identify patients who are likely to be responders to these drugs based on modes of action. There is preliminary data that this concept may be real and it is therefore an important question for trials to address in the future maybe in drug development where there is adequate power to obtain good data.
- None identified

REFERENCES


* Expert personal communication.