Secukinumab for ankylosing spondylitis – second line

SUMMARY

Secukinumab is intended to be used as second line therapy for the treatment of severe active ankylosing spondylitis (AS) in adults who have had an inadequate response to conventional therapy and/or tumour necrosis factor-α (TNF-α) inhibitors. If licensed, it would provide an additional treatment option for this patient group who currently have few effective options. Secukinumab is high-affinity fully human monoclonal antibody which specifically antagonises the interleukin 17A (IL-17A) receptor.

Spondyloarthropathies (SpAs) are one of the most common rheumatic diseases, with a prevalence of 0.5-1.9%. The most common SpA subgroups are AS (around 200,000 diagnosed cases of AS in the UK) and undifferentiated SpA. NICE estimate the prevalence of clinically significant AS at 0.15% of the population with an annual incidence of 6.9 per 100,000, representing approximately 2,300 new cases each year in England and Wales. AS typically affects young adults and is around three times more common in men than women, with men more likely to develop severe spinal disease. Approximately 1 in 10 people with AS have a severe form of the disease and about a third of people with AS may be unable to work, with a further 15% reporting some changes to their working lives. Patients with AS have an increased mortality risk, with a standardised mortality ratio of ≥1.5. Causes of death include cardiovascular disease, amyloidosis and fractures.

The treatment of AS includes a combination of patient/family education, pharmacological treatments, exercise, and physical therapy. Current pharmacological therapies include non-steroidal anti-inflammatory drugs and TNF-α inhibitors. Secukinumab is in two phase III clinical trials comparing its effect against treatment with placebo. These trials are expected to complete in 2014 and 2018.
**TARGET GROUP**

- Ankylosing spondylitis (AS): severe, active – second line; following inadequate response to conventional therapy and/or tumour necrosis factor-α (TNF-α) inhibitors.

**TECHNOLOGY**

**DESCRIPTION**

Secukinumab (AIN-457, KB-03303A) is a high-affinity fully human monoclonal antibody which specifically antagonises the interleukin 17A (IL-17A) receptor. IL-17A is a pro-inflammatory cytokine secreted exclusively by activated T-cells and is thought to be involved in autoimmunity. Secukinumab is intended for the treatment of severe active AS in adults who have had an inadequate response to conventional therapy and/or TNF-α inhibitors. It is administered by intravenous (IV) infusion as 3 loading doses of 10mg/kg at weeks 0, 2 and 4, followed by 75mg subcutaneous (SC) injections at week 8 and every 4 weeks thereafter.

Secukinumab is currently in the following phases of clinical trials for the stated indications:

**Phase III**
- Rheumatoid arthritis
- Plaque psoriasis.
- Psoriatic arthritis.
- Uveitis (adjunctive treatment).

**Phase II**
- Asthma.
- Multiple sclerosis (relapsing-remitting).
- Polymyalgia rheumatica.
- Crohn’s disease.
- Xerophthalmia.

**INNOVATION and/or ADVANTAGES**

If licensed, secukinumab would provide an additional treatment option for this patient group who currently have few effective options.

**DEVELOPER**

Novartis General Medicines.

**AVAILABILITY, LAUNCH OR MARKETING**

In phase III clinical trials.

**PATIENT GROUP**

**BACKGROUND**

AS is a chronic inflammatory condition that is strongly associated with the HLA-B27 genotype\(^1\). It is a progressive disease with onset typically in late teenage years and early
Diagnosis is based on clinical criteria, the modified New York Criteria\(^2\) and Assessments in Axial SpondyloArthritis international Society (ASAS) criteria\(^3\), and evidence of inflammation of the sacroiliac joints (sacro-ililitis) and/or inflammatory spinal disease on imaging (x-ray, MRI, bone scan)\(^4\).

Principal features are inflammation of the sacro-iliac joints and the vertebral bodies, affecting the whole spine in the worst cases. Inflammation at entheses can lead to new bone development and joint fixation (ankylosis)\(^2\). A significant number of patients have systemic involvement, including inflammation of the eyes (uveitis, 40\%\(^b\)); microscopic colitis; peripheral joint involvement (30\%); and heart and lung involvement; as well as weight loss and fatigue. Untreated disease results in pain, restriction of movement, spinal stiffness and postural changes, and in the longer term, fusion of the spinal vertebrae, increased risk of spinal fractures and osteoporosis causing considerable disability\(^5\).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to: The Musculoskeletal Services Framework (2006).

**CLINICAL NEED and BURDEN OF DISEASE**

An estimated 2\% of patients each year present to General Practice with back pain, and up to 5\% of these will show features of AS\(^6\). Spondyloarthropathies (SpAs) as a group are one of the most common rheumatic diseases with a prevalence of 0.5-1.9\%, making them roughly as common as rheumatoid arthritis\(^7\). The most common SpA subgroups are AS (around 200,000 diagnosed cases of AS in the UK\(^6\)) and undifferentiated SpA\(^7\). NICE estimate the prevalence of clinically significant AS at 0.15\% of the population with an annual incidence of 6.9 per 100,000, representing approximately 2,300 new cases each year in England and Wales\(^2\). AS is around three times more common in men than women, with men more likely to develop severe spinal disease\(^2\).

Approximately 1 in 10 people with AS have a severe form of the disease\(^6\). About a third of people with AS may be unable to work altogether, and a further 15\% report some changes to their working lives\(^2\). The loss of employment and work productivity adds substantially to the economic costs of AS\(^5\). It has been estimated that the number of people with AS in England eligible for treatment with biological drugs is around 20,000, however only around 30\% of these eligible patients will take up treatment\(^9\). Around two thirds of patients respond well to anti-TNF treatment, but for those who do not respond, treatment options are limited to another anti-TNF therapy or palliative care\(^4\). Patients with AS have an increased mortality risk, with a standardised mortality ratio of \(\geq 1.5\). Causes of death include cardiovascular disease, amyloidosis and fractures\(^2\). In 2011-12, there were 4,050 admissions for ankylosing spondylitis (ICD M45) in England resulting in 4,179 bed days and 4,108 finished consultant episodes\(^10\).

\(^{a}\) Expert personal communication.
\(^{b}\) Expert personal communication.
\(^{c}\) Expert personal communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


Other Guidance


EXISTING COMPARATORS and TREATMENTS

As AS manifestations can be varied, treatment choice depends on the patient’s symptoms and their severity. Guidelines for the management of AS suggest a combination of patient/family education, pharmacological treatments, exercise, physical therapy and very occasionally surgery.

Pharmacological therapies for AS include:
- NSAIDs – first line.
- Analgesics – for patients in whom NSAIDs are insufficient, contraindicated and/or poorly tolerated.
- Corticosteroid injections to the site of local musculoskeletal inflammation.
- Disease-modifying antirheumatic drugs (DMARDs) – no evidence for efficacy in axial disease, but may be considered in patients with peripheral arthritis.
- TNF-α inhibitor therapy – golimumab, adalimumab, etanercept and infliximab, for persistently high disease activity.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01358175, 2010-024529-18, CAIN457F2305; secukinumab vs placebo; phase III.</th>
<th>NCT01649375, 2012-000046-35, CAIN457F2310; secukinumab vs placebo; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Novartis Pharmaceuticals.</td>
<td>Novartis Pharmaceuticals.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
<td>Trial registry.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK).</td>
<td>EU and US.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
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</table>
### Participants

| n=348 (planned); aged ≥18 years; AS; moderate to severe; previous inadequate response to NSAIDs; patients who have been treated with TNF-α inhibitors (≤1) must have had an inadequate response. |
| n=222 (planned); aged ≥18 years; AS; moderate to severe; previous inadequate response to NSAIDs; patients who have been treated with TNF-α inhibitors (≤1) must have had an inadequate response. |

### Schedule

| Randomised to secukinumab 10mg/kg IV at weeks 0, 2, and 4, followed by secukinumab 75mg or 150mg, both SC at week 8 and every 4 weeks thereafter; or placebo IV at weeks 0, 2 and 4, followed by placebo SC at weeks 8 and 12. At week 16, patients are classified as responders or non-responders. Placebo responders: remain on placebo until week 24, then re-randomised to receive secukinumab 75mg or 150mg SC. Placebo non-responders: re-randomised to receive secukinumab 75mg or 150mg SC. |
| Randomised to secukinumab 75mg SC with placebo 150mg; or secukinumab 150mg SC with placebo 75mg SC; or placebo 75mg and 150mg, all once weekly at weeks 1, 2, 3, and 4, then every 4 weeks. At week 16, patients who were randomised to placebo at baseline are re-randomised to receive secukinumab 75mg with placebo 150mg; or secukinumab 150mg with placebo 75mg, both every 4 weeks for up to 5 years. |

### Follow-up

| Active treatment for 104 weeks. |
| Active treatment for 256 weeks, follow-up until week 268. |

### Primary outcome/s

| Assessment of SpondyloArthritis International Society (ASAS) 20d in TNF-α inhibitor naïve patients. |
| ASAS 20 in TNF-α inhibitor naïve patients. |

### Secondary outcome/s

| ASAS 20; ASAS 40; ASAS 40 in TNF-α inhibitor naïve patients; spinal mobility (BASM1 score). |
| ASAS 20; ASAS 40; ASAS 40 in TNF-α inhibitor naïve patients. |

### Expected reporting date

| Primary completion date reported as Jul 2014. |
| Primary completion date reported as Aug 2018. |

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### Notes

- **ASAS 20 response criteria** is defined as an improvement of at least 20% and absolute improvement of at least 10 units on a 0-100mm scale in at least 3 of 4 assessment domains (1. Subject’s global assessment of disease activity. 2. Subject’s assessment of inflammatory back pain. 3. Function represented by Bath Ankylosing Spondylitis Functional Index Visual Analog Scale (BASFI VAS). 4. Morning stiffness represented by the last 2 questions on the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]).
- **Bath Ankylosing Spondylitis Metrology Index.**
All administered on days 1 and 22, followed by 25 week observation period.

Follow-up

Active treatment up to 1 year.

Follow-up Active treatment period 6 weeks; then up to 28 weeks follow-up.

Primary outcome/s

Safety and tolerability. ASAS 20.

Secondary outcome/s

Immunogenicity; total blood IL-17 concentration; pharmacokinetics. ASAS 40; ASAS 5/6; disease activity; quality of life; 44-joint count; Maastricht Ankylosing Spondylitis Enthesis Score.

Key results

Interim analysis for secukinumab vs placebo: ASAS 20, 14/23 patients (60.9%) vs 1/6 patients (16.7%) (probability of positive treatment difference = 99.8%). For secukinumab group, ASAS 40, 30%; ASAS 5/6, 35%; mean BASDAI change, -1.8 (-5.6 to 0.8).

Adverse effects (AEs)

Most common AEs in secukinumab group included headache (29%), nasopharyngitis (29%), pyrexia (17%), nausea (17%), diarrhoea (17%), and infection (71%). There were 2 serious AEs reported (1 patient each on placebo and secukinumab); 2 people discontinued due to AEs (1 patient each on placebo and secukinumab).

Expected reporting date

Primary completion date reported as Dec 2012. Previously reported as May 2011.

ESTIMATED COST and IMPACT

COST

The cost of secukinumab is not yet known. The cost of selected comparator treatments for AS are summarised below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Annual cost £ (11)</th>
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<tbody>
<tr>
<td>Adalimumab</td>
<td>40mg SC every 2 weeks.</td>
<td>£9,295</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25mg SC twice weekly, or 50mg once weekly.</td>
<td>£9,295</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5mg/kg IV at week 0, 2 and 6, then every 6-8 weeks.</td>
<td>£11,700 - £15,100 (9)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50mg SC once monthly.</td>
<td>£9,155.64</td>
</tr>
</tbody>
</table>

IMPACT - SPECULATIVE

Impact on Patients and Carers

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

1 ASAS 5 out of 6 (5/6) response criteria is defined as an improvement of ≥20% in at least 5 out of the following 6 domains: pain, patient global, function, inflammation, spinal mobility (measured by BASMI) and acute phase reactants (by C-reactive protein).

9 Based on an adult weight of 75kg.
Impact on Services

☑ Increased use of existing services: IV loading doses may require additional day unit capacity.
☐ 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 existing treatments.
☐ None identified

Other Issues

☑ Clinical uncertainty or other research question identified: Expert opinion suggests that more data on the outcomes BASDAI and BASFI, and safety is required. Expert opinion also suggests there is clinical uncertainty surrounding the ability of anti-IL17s to prevent or reverse radiographic progression and that research should be continued to long term follow-up with radiographic outcomes. Early treatment with anti-TNFs given on the basis of MRI is about twice as effective in inducing remission as late treatment given after the development of x-ray changes21. Therefore, expert opinion suggests research should also consider the use of secukinumab as an early treatment option. In addition, expert opinion proposes further investigation into whether anti-IL17 or other therapies alone, sequentially, or in combination would have greater efficacy than anti-TNFs in attaining remission. It is also suggested that additional research is required to investigate the capacity of patients to return to or be maintained in the workplace for those who are on maintenance secukinumab therapy
☐ None identified

REFERENCES


h Expert personal communication.
NIHR Horizon Scanning Centre

5 NIHR Horizon Scanning Centre. Certolizumab pegol (Cimzia) for the treatment of ankylosing spondylitis – second or third line. Birmingham: NIHR HSC; August 2011.