Secukinumab for moderate to severe, active rheumatoid arthritis.

SUMMARY

Secukinumab is intended to be used in combination with methotrexate (MTX) for the treatment of moderate to severe active rheumatoid arthritis (RA) in patients who have either responded inadequately, or who were intolerant to, previous therapy with tumour necrosis factor (TNF) antagonists.

RA affects around 1% of the population (over 580,000 people) in England and Wales. The annual incidence of RA is 1.5 per 10,000 in males and 3.6 per 10,000 in females, which equates to approximately 12,000 new diagnoses each year in the UK. RA can lead to progressive disability and a decrease in quality of life. Approximately one third of people stop work because of the disease within 2 years of onset, and after 10 years, 30% of patients are severely disabled. The life expectancy of people with RA is reduced by 5-10 years; 35-50% of this excess risk is accounted for by cardiovascular mortality.

TNF inhibitors (such as etanercept, infliximab, adalimumab, golimumab and certolizumab pegol) and tocilizumab in combination with MTX, are recommended for moderate to severe active RA after failure of at least two conventional disease modifying anti-rheumatic drugs (DMARDs), including MTX. Secukinumab is currently in 2 phase III clinical trials comparing its effect on clinically important improvements in arthritis outcomes against treatment with placebo or abatacept. Both trials are expected to complete in August 2013.
TARGET GROUP

- Rheumatoid Arthritis (RA): active, moderate to severe – in patients who have either responded inadequately to, or were intolerant to, previous therapy with TNF antagonists; likely to be in combination with MTX.

TECHNOLOGY

DESCRIPTION

Secukinumab (AIN-457, AIN-457A, KB-03303A, NVP-AIN-457) 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 moderate to severe active RA and is administered by intravenous infusion as 3 loading doses of 10mg/kg, followed by 75mg or 150mg subcutaneous injections every 4 weeks, and is likely to be given in combination with MTX.

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

Phase III
- Ankylosing spondylitis (treatment experienced patients).
- Plaque psoriasis.
- Psoriatic arthritis.

Phase II
- Behcet's disease.
- Uveitis (adjunctive treatment).
- Asthma.
- Multiple sclerosis (relapsing-remitting).
- Polymyalgia rheumatica.
- Xerophthalmia.

INNOVATION and/or ADVANTAGES

If licensed, secukinumab may provide an additional treatment option for this patient group.

DEVELOPER

Novartis Pharmaceuticals UK Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.
PATIENT GROUP

BACKGROUND

RA is a chronic, inflammatory, multisystem, progressive autoimmune disease. Synovial joints, typically the small joints of the hands and feet, are often affected bilaterally and symmetrically. Clinical features of synovitis usually include pain (usually worse after periods of rest or inactivity), swelling, stiffness and loss of function. On palpation, affected joints are tender, warm and give a ‘boggy’ feel. Extra-articular presentations may include lymphadenopathy or involvement of other body systems, whilst systemic features include malaise, fatigue, fever and weight loss. Other presenting features of RA include rheumatoid nodules (over extensor surfaces, which occur in approximately one third of patients). Symptoms may be insidious, palindromic (waxing and waning) or explosive in onset. Rarely, patients may present with fever, joint pain or weight loss. A family history of RA is considered a risk factor for developing the disease.

NHS or GOVERNMENT PRIORITY AREA

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

CLINICAL NEED and BURDEN OF DISEASE

RA affects around 1% of the population (over 580,000 people) in England and Wales. The annual incidence of RA is 1.5 per 10,000 in males and 3.6 per 10,000 in females, which equates to approximately 12,000 new diagnoses each year in the UK. Peak age of onset is 40-70 years and the disease is severe in around 15% of patients. It has been estimated that around 10% of patients with RA (approximately 34,600 people) require treatment with biological therapies after the failure of conventional disease-modifying anti-rheumatic drugs (DMARDs). In 2010-11, there were 56,630 inpatient admissions for RA (ICD10 M05, 06) in NHS hospitals in England resulting in 58,145 finished consultant episodes and 46,720 bed days.

RA can lead to progressive disability and a decrease in quality of life. Approximately one third of people stop work because of the disease within 2 years of onset, and after 10 years, 30% of patients are severely disabled. The life expectancy of people with RA is reduced by 5-10 years; 35-50% of this excess risk is accounted for by cardiovascular mortality. The total costs of RA in the UK, including indirect costs and work-related disability, have been estimated at between £3.80 and £4.75 billion per year.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

• NICE technology appraisal. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. (TA225). 2011\textsuperscript{13}.
• NICE technology appraisal. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after failure of a TNF inhibitor. (TA195). 2010\textsuperscript{2}.
• NICE technology appraisal. Certolizumab pegol for the treatment of rheumatoid arthritis. (TA186). 2010\textsuperscript{14}.
• NICE technology appraisal. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. (TA130). 2010\textsuperscript{15}.
• NICE clinical guideline. Rheumatoid arthritis: The management of rheumatoid arthritis in adults. (CG79). 2009\textsuperscript{6}.

Other Guidance

• British Society of Rheumatology (BSR). Top ten quality standards for RA. 2012\textsuperscript{16}.
• Scottish Intercollegiate Guidelines Network. Management of early rheumatoid arthritis. (CG123). 2011\textsuperscript{17}.
• European League Against Rheumatism (EULAR). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. 2010\textsuperscript{18}.
• BSR & British Health Professionals in Rheumatology (BHPR). BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. 2010\textsuperscript{19}.
• Royal College of Nursing. Assessing, managing and monitoring biologic therapies for inflammatory arthritis, guidance for rheumatology practitioners. 2009\textsuperscript{20}.
• Prodigy (formerly CKS). Rheumatoid arthritis. 2009\textsuperscript{21}.
• BSR and BHPR. Disease-modifying anti-rheumatic drug (DMARD) therapy. 2008\textsuperscript{22}.
• BSR and BHPR. BSR and BHPR guideline for the management of Rheumatoid Arthritis (The first 2 years). 2006\textsuperscript{23}.
• BSR. Update on the British Society for Rheumatology guidelines for prescribing TNF\textsubscript{\alpha} blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). 2005\textsuperscript{24}.
• BSR. BSR guidelines on standards of care for persons with rheumatoid arthritis. 2005\textsuperscript{25}.

EXISTING COMPARATORS and TREATMENTS

The goal of management in early disease is to suppress disease, control pain, reduce functional limitation, reduce risk of permanent joint damage and achieve clinical remission\textsuperscript{3,19}. The clinical management of RA includes physical therapy, surgical interventions and a range of pharmacological treatments including\textsuperscript{2,8}:

Non-biologic therapies
• Corticosteroids.
• Non-steroidal anti-inflammatory drugs (NSAIDs).
• Cyclo-oxygenase-2 (COX-2) inhibitors.
• Conventional DMARDs, including MTX, sulfasalazine, leflunomide and azathioprine (first line treatment). Usually administered within three months of diagnosis to stabilise joint function, either as combination therapy (MTX and at least one other conventional DMARD) or as monotherapy (when combination therapy inappropriate)\textsuperscript{6,a}.

\textsuperscript{a} Expert personal opinion suggests that despite NICE guidance, monotherapy is often used first: combination therapy is used if there is no response.
Biologic DMARDs

- TNF inhibitors, such as etanercept, infliximab, adalimumab, golimumab and certolizumab pegol, and tocilizumab in combination with MTX, are recommended for moderate to severe active RA after failure of at least two conventional DMARDs, including MTX. If MTX is unsuitable, tocilizumab, adalimumab, etanercept, and certolizumab pegol may be used as monotherapy.

- Rituximab in combination with MTX is recommended for patients with severe active RA who have had an inadequate response to, or are intolerant of other DMARDs, including at least one TNF inhibitor. Where rituximab is unsuitable or ineffective, tocilizumab, golimumab, etanercept, infliximab, adalimumab and abatacept may be used in combination with MTX. Adalimumab or etanercept may be used as monotherapy if MTX is unsuitable.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01377012; secukinumab (75mg or 150mg) vs placebo; phase III.</th>
<th>NCT01350804; secukinumab (75mg or 150mg) vs abatacept or placebo; phase III.</th>
<th>NCT00928512; secukinumab vs placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
<td>Published.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>EU (excl UK), USA and other countries</td>
<td>EU, USA and other countries.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=630 (planned); ≥18 years; RA; disease activity criteria defined by ≥6/68 tender joints and ≥6/66 swollen joints; anti-cyclic citrullinated peptide (CCP) antibodies positive OR rheumatoid factor positive WITH at least hsCRP ≥ 10mg/L OR ESR ≥ 28mm/1st hr; receiving at least one anti-TNF-α agent for ≥3 months before randomisation and have experienced an inadequate response to treatment or experienced intolerance to ≥1 anti-TNF-α agent; receiving MTX ≥3 months before randomisation and on a stable dose ≥4 weeks before randomisation (7.5 to 25 mg/week).</td>
<td>n=548 (planned); ≥18 years; RA; ≥3 months before screening; baseline disease activity criteria defined by ≥6/68 tender joints and ≥6/66 swollen joints; anti-cyclic citrullinated peptide (Anti-CCP) antibodies positive OR rheumatoid factor positive WITH at least hsCRP ≥10mg/L OR ESR ≥28mm/1st hr; receiving at least one anti-TNF-α agent ≥3 months before randomisation and have experienced an inadequate response to treatment or have experienced intolerance to ≥1 anti-TNF-α agent; receiving MTX or one other DMARD for ≥3 months before randomisation at a stable dose ≥4 weeks before randomisation (7.5 to 25 mg/week for MTX, other DMARD at maximum tolerated dose).</td>
<td>n=237; ≥18 years; RA; baseline disease activity criteria defined by ≥6/28 tender joints and ≥6/28 swollen joints WITH either hsCRP ≥10 mg/L OR ESR ≥ 28 mm/1st hr; patients on MTX for ≥3 months and treated with stable dose of MTX (7.5-25 mg/week) for at least 4 weeks; previous biologic use allowed: approximately 20% of patients were previously exposed.</td>
</tr>
</tbody>
</table>
### Schedule

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Randomised to secukinumab 10mg/kg at weeks 0, 2 and 4, followed by secukinumab 75mg SC at week 8 and every 4 weeks thereafter; or secukinumab 10mg/kg at weeks 0, 2 and 4, followed by secukinumab 150mg SC at week 8 and every 4 weeks thereafter; or placebo IV at weeks 0, 2 and 4, followed by SC at week 8 and every 4 weeks thereafter.</td>
</tr>
<tr>
<td>2</td>
<td>Randomised to secukinumab 10mg/kg at weeks 0, 2 and 4, followed by secukinumab 75mg SC at week 8 and every 4 weeks thereafter; or secukinumab 10mg/kg at weeks 0, 2 and 4, followed by secukinumab 150mg SC at week 8 and every 4 weeks thereafter; placebo IV at weeks 0, 2 and 4, followed by SC at week 8 and every 4 weeks thereafter; placebo IV at weeks 0, 2 and 4, followed by SC at week 8 and every 4 weeks thereafter; placebo IV at weeks 0, 2 and 4, followed by SC at week 8 and every 4 weeks thereafter; abatacept IV at weeks 0, 2, 4 and every 4 week thereafter; abatacept IV at weeks 0, 2 and 4 and every 4 week thereafter.</td>
</tr>
<tr>
<td>3</td>
<td>Randomized in 1:1:1:1 ratio to secukinumab 300 mg, 150 mg, 75 mg, 25 mg, or placebo SC every 4 weeks.</td>
</tr>
</tbody>
</table>

### Follow-up

- **24 weeks**, with additional follow-up to 2 years.
- **24 weeks**, with additional follow-up to 1 year.
- To week 60.

### Primary outcome/s

- ACR20\(^b\) at 24 weeks.
- ACR20 at 24 weeks.
- ACR20 at 16 weeks.

### Secondary outcome/s

- HAQ-DI\(^c\) at 24 weeks; SvH\(^d\) at 24 weeks; ACR70 at 1 year.
- HAQ-DI at 24 weeks; ACR70 at 1 year; ACR70 at 1 year.
- ACR20 at 8 weeks; ACR50; ACR70; DAS28\(^e\) at 16 weeks; individual ACR components, including markers of inflammation (hsCRP and ESR); immunogenicity; pharmacokinetics and pharmacodynamics; quality of life and fatigue.

### Key results

- The proportion of ACR20 responders at week 16 with secukinumab 25-300mg was 36.0-53.7% (placebo 34%). Clinically relevant and statistically significant decreases in CRP with secukinumab 75–300 mg versus placebo.

### Adverse effects

- Most adverse events (AE) were mild to moderate in...  

---

\(^b\) ACR: the American College of Rheumatology criteria are a core set of six outcome variables for the assessment of clinically important improvement: physical global assessment of disease activity; patient global assessment of overall well-being; functional ability; number of joints with active arthritis; number of joints with limited range of motion; and ESR. ACR20, ACR50 and ACR70 represent a 20%, 50% and 70% improvement in at least three response criteria (with no more than one response variable worse by greater than 30%).

\(^c\) Health Assessment Questionnaire Disability Index (HAQ-DI).

\(^d\) van der Heijde total modified Sharp score (SvH): radiographic scoring method in RA.

\(^e\) Disease Activity Score 28 (DAS28): joint assessment for swelling and tenderness.
severity. Infections were slightly more frequent with secukinumab than placebo. Six serious AE were reported: secukinumab 75 mg (one), secukinumab 300 mg (four) and placebo (one).

<table>
<thead>
<tr>
<th>Expected reporting date</th>
<th>Estimated primary completion date reported as August 2013.</th>
<th>Estimated primary completion date reported as August 2013.</th>
<th>Study completed March 2012.</th>
</tr>
</thead>
</table>

## ESTIMATED COST and IMPACT

### COST

The cost of secukinumab is not yet known. The cost of selected comparator treatments are as follows\(^5\,30\).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golimumab</td>
<td>50mg subcutaneous (SC) injection once monthly.</td>
<td>£9,156</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25mg SC twice weekly or 50mg SC once weekly.</td>
<td>£9,295</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40mg SC every 2 weeks.</td>
<td>£9,156</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3mg/kg IV at weeks 0, 2 and 6, then every 8 weeks thereafter.</td>
<td>£11,330 - £12,589(^1).</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>400mg SC at weeks 0, 2 and 4, then 200mg every 2 weeks.</td>
<td>£10,368 for first year. £9,925 for subsequent years.</td>
</tr>
<tr>
<td>Abatacept(^9)</td>
<td>750mg IV at weeks 0, 2 and 4, then every 4 weeks thereafter.</td>
<td>£13,608</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

#### 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

\(^1\) Based on average weight of 77.9kg.
\(^2\) NICE guidance: Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (August 2011) states that abatacept is not recommended for the treatment of moderate to severe active RA in adults who have had an inadequate response to one or more DMARD, including methotrexate\(^8\).
Impact on Costs

- 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:
- None identified

REFERENCES


23 British Society of Rheumatology (BSR) & British Health Professionals in Rheumatology (BHPR). BSR and BHPR guideline for the management of Rheumatoid Arthritis (The first 2 years). London: BSR; July 2006.


