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Newcastle University

Health Technology Briefing
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Tocilizumab biosimilar for treating moderate to severe active rheumatoid arthritis

Company/Developer	Celltrion Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 35780	NICE ID: 11848	UKPS ID: 669315

Licensing and Market Availability Plans

Currently in phase III clinical trial.

Summary

Tocilizumab biosimilar is in clinical development for the treatment of moderate to severe, active rheumatoid arthritis (RA). RA is an autoimmune disease which means the immune system mistakenly attack the cells that line your joints, which makes them swollen, stiff and painful. This can affect and damage nearby bones and tissue. The causes of RA are not clearly known but there is an increased risk associated with women, having a family history of RA, or smoking. Symptoms vary but include joint pain, swelling around joint(s) and stiffness. General symptoms include feeling extremely tired, flu-like symptoms and weight loss. A biosimilar medicine is a biological medicine which has not shown any clinically meaningful differences in quality, safety, and efficacy from the reference medicine. Increasing the availability of biosimilar medicines allows the National Health Service to take advantage of up to £300m of savings each year, enabling more patients to have access to other life-saving and life-enhancing treatments.

Tocilizumab biosimilar contains the active ingredient tocilizumab, which is a recombinant humanised monoclonal antibody (protein). Tocilizumab binds to and blocks the action of an anti-inflammatory protein known as interleuekin-6 (IL-6), which reduces the inflammation that causes the symptoms of RA. Tocilizumab biosimilar will be administered as an intravenous (IV) infusion. If approved, tocilizumab biosimilar may offer a more affordable option to the reference medicine tocilizumab for patients with moderate to severe active RA.

Proposed Indication

Treatment of adults aged 18 to 75 years old with moderate to severe active rheumatoid arthritis (RA).[1]

Technology

Description

Tocilizumab biosimilar (CT-P47) contains the active ingredient tocilizumab, is a recombinant humanised monoclonal antibody that is being developed as a similar biological medicinal product to tocilizumab (RoActemra/Actemra).[1] Tocilizumab binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes, and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.[2] A biosimilar medicine is a biological medicine which has been shown not to have any clinically meaningful differences from the originator medicine in terms of quality, safety and efficacy.[3]

Tocilizumab biosimilar is in clinical development for the treatment of moderate to severe active RA. In the phase III trial (NCT05489224), tocilizumab biosimilar 8mg/kg (not exceeding an 800mg dose) will be administered as an intravenous (IV) infusion once every 4 weeks (Q4W).[1]

Key Innovation

Biological medicines are currently the largest cost and cost growth area in the National Health Service (NHS) medicines budget.[3] Biosimilars are more cost-effective versions of biologics, as they lead to price competition that improves patient access to safe and effective biological medicines and help health systems with restricted budgets.[3,4] Biosimilars could help alleviate some of the financial burden of care while still providing the same benefits of originator biologic treatments.[5] Through making biosimilar medicines more quickly available, the NHS will be able to take advantage of up to £300m of savings each year offered by these new products, enabling more patients to have access to other life-saving and life-enhancing treatments.[3] If approved, tocilizumab biosimilar would offer an additional treatment option for moderate to severe active RA patients.

Regulatory & Development Status

Tocilizumab biosimilar does not currently have Marketing Authorisation in the EU/UK for any indication.

Tocilizumab is currently licensed in the UK for the following indications:[2,6]

- In combination with methotrexate, or as monotherapy (in case of intolerance to methotrexate or where continued treatment with methotrexate is inappropriate) for the treatment of RA in adults
- Adults with coronavirus disease 2019 (COVID-19)
- Active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older
- In combination with methotrexate for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older
- Chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.
- Giant Cell Arteritis (GCA) in adult patients.

Patient Group

Disease Area and Clinical Need

RA is an autoimmune disease. The immune system attacks the thin layer of cells (synovium) that line your joints by mistake, making them swollen, stiff and painful and releasing chemicals that damage nearby bones, cartilage, ligaments and tendons.[7,8] The hands, feet and wrists are commonly affected, but it can also cause problems in other parts of the body. It's not clear what triggers this problem with the immune system, although there is an increased risk for women, having a family history of RA, or smoking.[7] RA affects joints and also causes more general symptoms. Symptoms vary from person to person. They often begin quite slowly, affecting just a few joints, but for some people, the condition develops more quickly. Symptoms affecting joints include pain, which is usually worse when resting or inactive, swelling around joint(s), and stiffness, especially first thing in the morning or if inactive for a long time. General symptoms include feeling extremely tired (fatigued), flu-like symptoms such as a fever, feeling generally unwell, and weight loss.[9]

The incidence of RA is low, with around 1.5 men and 3.6 women developing RA per 10,000 people per year.[10] RA affects around 400,000 people in the UK. It can affect adults at any age, but most commonly starts between the ages of 40 and 50. About three times as many women as men are affected.[7] Approximately one-third of people stop work because of the disease within two years of onset, and this increases thereafter.[10] In England (2021-22), there were 24,418 finished consultant episodes (FCEs) and 24,025 admissions for a primary diagnosis of seropositive RA (ICD-10 code M05), which resulted in 22,694 day cases and 3,615 FCE bed days. There was also 35,221 FCEs and 33,933 admissions for a primary diagnosis of other RA (ICD-10 code M06), which resulted in 30,638 day cases and 11,928 FCE bed days.[11]

Recommended Treatment Options

There is no cure for rheumatoid arthritis. The main treatment options include: medicine that is taken long term to relieve symptoms and slow the progress of the condition, supportive treatments such as physiotherapy and occupational therapy and surgery to correct any joint problems that develop.[12]

For newly diagnosed RA, the National Institute for Health and Care Excellence (NICE) recommend first-line treatment with conventional disease-modifying antirheumatic drugs (DMARD) monotherapy which includes oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms.[10] Methotrexate is usually the first medicine given for rheumatoid arthritis, often with another DMARD and a short course of corticosteroids to relieve any pain. These may be combined with biological treatments, such as adalimumab, etanercept and infliximab. Biological medicines are usually taken in combination with methotrexate or another DMARD, and are usually only used if DMARDs have not been effective on their own.[13] Short-term treatment with glucocorticoids is recommended for managing flares in adults with recent-onset or established disease to rapidly decrease inflammation. For symptom control, oral non-steroidal anti-inflammatory drugs (NSAIDs, including traditional NSAIDs and cox II selective inhibitors) are also recommended when control of pain or stiffness is inadequate.[10]

Other treatments recommended by NICE for moderate to severe active RA in adults whose disease has responded inadequately to conventional DMARD therapy include: upadacitinib, adalimumab, etanercept, infliximab, abatacept, filgotinib, sarilumab, tofacitinib, baricitinib, rituximab, golimumab, certolizumab pegol and tocilizumab.[14-22]

Clinical Trial Information

Trial	NCT05489224; EudraCT- 2022-001066-36; A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of Two Intravenous Infusion Formulations of Tocilizumab (CT-P47 and RoActemra) When Co-administered With Methotrexate in Patients With Rheumatoid Arthritis **Phase III –** Not yet recruiting **Primary completion date –** August 2023
Trial Design	Randomised, parallel assignment, quadruple masked
Population	N = 448 (estimated); diagnosis of RA according to the 2010 ACR/EULAR classification criteria for at least 24 weeks prior to the first administration of the study drug; aged 18 to 75 years
Intervention(s)	Tocilizumab biosimilar 8mg/kg (not exceeding 800mg/dose) by IV infusion Q4W
Comparator(s)	RoActemra, 8 mg/kg (not exceeding 800 mg/dose) by IV infusion Q4W
Outcome(s)	Primary outcome measures: • Mean Change from Baseline in Disease Activity Score 28 (DAS28) using Erythrocyte Sedimentation Rate (ESR) [Time Frame: Week 12] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of tocilizumab biosimilar is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Upadacitinib for treating moderate rheumatoid arthritis (TA744). November 2021.
- NICE technology appraisal. Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed (TA715). July 2021.
- NICE technology appraisal. Filgotinib for treating moderate to severe rheumatoid arthritis (TA676). February 2021.
- NICE technology appraisal. Upadacitinib for treating severe rheumatoid arthritis (TA665). December 2020.
- NICE technology appraisal. Sarilumab for treating moderate to severe rheumatoid arthritis (TA485). November 2017.
- NICE technology appraisal. Tofacitinib for moderate to severe rheumatoid arthritis (TA480). October 2017.

- NICE technology appraisal. Baricitinib for moderate to severe rheumatoid arthritis (TA466). August 2017.
- NICE technology appraisal guidance. Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (TA415). October 2016.
- NICE technology appraisal. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (TA375). January 2016.
- NICE technology appraisal. Tocilizumab for the treatment of rheumatoid arthritis (TA247). February 2012.
- NICE technology appraisal. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs (TA225). June 2011.
- NICE technology appraisal. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (TA195). August 2010.
- NICE guideline. Rheumatoid arthritis in adults: management (NG100). July 2018, last updated: October 2020.
- NICE quality standard. Rheumatoid arthritis in over 16s (QS33). June 2013, last updated: January 2020.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.

Other Guidance

- American College of Rheumatology. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. June 2021.[23]
- European Alliance of Associations for Rheumatology. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. January 2020.[24]
- The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR). BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. June 2017.[25]

Additional Information

References

1 ClinicalTrials.gov. *A Study to Compare Efficacy and Safety of CT-P47 and RoActemra in Patients With Rheumatoid Arthritis. Trial ID: NCT05489224*. 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT05489224 [Accessed 13th January 2023].

2 Electronic Medicines Compendium. *RoActemra 20mg/ml Concentrate for Solution for Infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/6673/ [Accessed 13th January 2023].

3 NHS England. *Biosimilar medicines.* 2022. Available from: https://www.england.nhs.uk/medicines-2/biosimilar-medicines/ [Accessed 13th January 2023].

4 Ascef BdO, Lopes ACdF, de Soárez PC. Health technology assessment of biosimilars worldwide: a scoping review. *Health Research Policy and Systems*. 2020;18(1):95. Available from: https://doi.org/10.1186/s12961-020-00611-y.
5 Kvien TK, Patel K, Strand V. The cost savings of biosimilars can help increase patient access and lift the financial burden of health care systems. *Seminars in Arthritis and Rheumatism*. 2022;52:151939. Available from: https://doi.org/10.1016/j.semarthrit.2021.11.009.
6 Electronic Medicines Compendium. *RoActemra 162 mg Solution for Injection in Pre-Filled Syringe*. 2022. Available from: https://www.medicines.org.uk/emc/product/5357/smpc#INDICATIONS [Accessed 17th January 2023].
7 NHS Inform. *Rheumatoid arthritis*. 2022. Available from: https://www.nhsinform.scot/illnesses-and-conditions/muscle-bone-and-joints/conditions/rheumatoid-arthritis [Accessed 13th January 2023].
8 National Health Serivce (NHS). *Causes-Rheumatoid arthritis*. 2019. Available from: https://www.nhs.uk/conditions/rheumatoid-arthritis/causes/ [Accessed 13th January 2023].
9 Bupa UK. *Rheumatoid arthritis*. 2023. Available from: https://www.bupa.co.uk/health-information/muscles-bones-joints/rheumatoid-arthritis [Accessed 13th January 2023].
10 National Institute for Health and Care Excellence. *Rheumatoid arthritis in adults: management*. 2018. Available from: https://www.nice.org.uk/guidance/ng100/resources/rheumatoid-arthritis-in-adults-management-pdf-66141531233989 [Accessed 13th January 2023].
11 NHS Digital. *Hospital Admitted Patient Care Activity 2021-22: Diagnosis*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 17th January 2023].
12 National Health Serivce (NHS). *Overview-Rheumatoid arthritis*. 2019. Available from: https://www.nhs.uk/conditions/rheumatoid-arthritis/ [Accessed 13th January 2023].
13 National Health Serivce (NHS). *Treatment-Rheumatoid arthritis*. 2019. Available from: https://www.nhs.uk/conditions/rheumatoid-arthritis/treatment/ [Accessed 13th January 2023].
14 National Institute for Health and Care Excellence. *Upadacitinib for treating moderate rheumatoid arthritis*. 2021. Available from: https://www.nice.org.uk/guidance/ta744/chapter/1-Recommendations [Accessed 13th January 2023].
15 National Institute for Health and Care Excellence. *Upadacitinib for treating severe rheumatoid arthritis*. 2020. Available from: https://www.nice.org.uk/guidance/ta665/chapter/1-Recommendations [Accessed 13th January 2022].
16 National Institute for Health and Care Excellence. *Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed*. 2021. Available from: https://www.nice.org.uk/guidance/ta715/chapter/1-Recommendations [Accessed 13th January 2023].
17 National Institute for Health and Care Excellence. *Filgotinib for treating moderate to severe rheumatoid arthritis*. 2021. Available from: https://www.nice.org.uk/guidance/ta676/chapter/1-Recommendations [Accessed 13th Janaury 2023].
18 National Institute for Health and Care Excellence. *Sarilumab for moderate to severe rheumatoid arthritis*. 2017. Available from:

https://www.nice.org.uk/guidance/ta485/chapter/1-Recommendations [Accessed 13th January 2023].

19 National Institute for Health and Care Excellence. *Tofacitinib for moderate to severe rheumatoid arthritis.* 2017. Available from: https://www.nice.org.uk/guidance/ta480/chapter/1-Recommendations [Accessed 13th January 2023].

20 National Institute for Health and Care Excellence. *Baricitinib for moderate to severe rheumatoid arthritis.* 2017. Available from: https://www.nice.org.uk/guidance/ta466/chapter/1-Recommendations [Accessed 13th January 2023].

21 National Institute for Health and Care Excellence. *Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor.* 2020. Available from: https://www.nice.org.uk/guidance/ta195/chapter/1-Guidance [Accessed 13th January 2023].

22 National Institute for Health and Care Excellence. *Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed.* 2016. Available from: https://www.nice.org.uk/guidance/ta375/chapter/1-Recommendations [Accessed 13th January 2023].

23 Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol.* 2021;73(7):1108-23. Available from: https://doi.org/10.1002/art.41752.

24 Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79(6):685-99. Available from: https://doi.org/10.1136/annrheumdis-2019-216655.

25 Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology.* 2017;56(6):865-8. Available from: https://doi.org/10.1093/rheumatology/kew479.

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