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Health Technology Briefing
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Otilimab in combination with conventional synthetic DMARDs for treating rheumatoid arthritis

Company/Developer	GlaxoSmithKline UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27284	NICE TSID: 10453	UKPS ID: 664289

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Otilimab in combination with conventional synthetic disease-modifying antirheumatic drugs (DMARDs) is in clinical development for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), who have had an inadequate response to conventional synthetic DMARDs and/or targeted therapies (biologic DMARDs and Janus Kinase inhibitors). RA is a chronic autoimmune condition where the body's immune system attacks the joints. It most commonly affects the hands, feet and wrists but can affect any joint on the body, resulting in pain, swelling and difficulty moving. The active disease is often characterised by 'flares', where symptoms worsen for a period of time. Medications such as conventional synthetic DMARDs and/or targeted therapies may help control the symptoms and slow the rate of progression. However, some people may have an inadequate response to these treatments and are left with limited options.

Otilimab is a monoclonal antibody that works by blocking the granulocyte macrophage colony-stimulating factor (GM-CSF), a protein that is produced by the body that leads to inflammation, pain and joint damage. Through this action, otilimab eliminates the biological mechanism of RA that results in its symptoms. Otilimab is administered weekly via subcutaneous injection, in combination with conventional synthetic DMARDs. If licensed, otilimab will offer a new treatment option for adult patients with moderately to severely active RA who have had an inadequate response to conventional synthetic DMARDs and/or targeted therapies.

Proposed Indication

Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have an inadequate response to other therapies.[1-3]

Technology

Description

Otilimab (GSK-3196165) is an investigational anti-granulocyte macrophage colony-stimulating factor (anti GM-CSF) monoclonal antibody. GM-CSF is a protein that plays a central role in a broad range of immune-mediated diseases, including rheumatoid arthritis and it acts on cells, including macrophages that can lead to inflammation, joint damage, and pain. Otilimab inhibits the biological function of GM-CSF by blocking the interaction of GM-CSF with its cell surface receptor.[4]

Otilimab is in clinical development for the treatment of adult patients with moderate to severe RA who have inadequate response to DMARDs or targeted therapies.[4] In the phase III clinical studies contRAst 1, 2 and 3 (NCT03980483, NCT03970837, NCT04134728), otilimab will be administered via subcutaneous (SC) injection once weekly in combination with a stable dose of a conventional synthetic DMARDs (csDMARDs).[1-3]

Key Innovation

Despite the use of DMARDs, of which methotrexate is considered the standard of care, a substantial proportion of patients either fail to respond or have an inadequate response to the treatment. This results in a gap in the current treatment options for patients with moderate to severe active RA.[4]

If licensed, otilimab will provide a new targeted therapy, specific for GM-CSF (granulocyte-macrophage colony-stimulating factor), and so will offer a new treatment option for patients who have had an inadequate response to csDMARDs, biologic DMARDs and/or Janus Kinase inhibitors.[4]

Regulatory & Development Status

Otilimab does not currently have marketing authorisation in the EU/UK for any indication.

Patient Group

Disease Area and Clinical Need

Rheumatoid Arthritis (RA) is a chronic, systemic inflammatory condition characterised by pain, joint swelling, stiffness, joint destruction and disability[4] The condition usually affects the hands, feet, and wrists but can affect any synovial joint in the body and can include extra-articular manifestations. RA is a chronic autoimmune condition where the immune system attacks the tissue that surrounds the joints (synovium), resulting in pain and inflammation and can lead to destruction of the adjoining bones, cartilage, tendons and ligaments.[5] RA is characterised by flare ups where symptoms are worse (active disease), these can often be controlled/ reduced in duration and frequency by medication. In moderate to severe cases attacks are less controlled by medication. RA can be associated with severe symptoms/ complications at any stage such as cardiovascular disease, increased risk of heart attack or stroke, depression, carpal tunnel syndrome, serious infections, and increased mortality.[6,7] There is no known cause of RA but there are some known risk factors such as genetics, hormones (women are at a higher risk), or smoking[5,6]

RA affects roughly 1% of the UK population, with around 1.5 men and 3.6 women per 100,000 developing the condition per year. Onset of RA can occur at any age but peaks between people aged 30-50 years old. 70–80-year-olds experience the highest number of active disease incidences. One-third of people have to stop working due to RA symptoms within 2 years of onset with this number increasing with time.[8] In England (2020-21), there were 22,680 finished consultant episodes (FCE) for RA, unspecified(ICD-10 code: M06.9), with 21,955 hospital admissions of which 19,122 were day cases and 5,703 were FCE bed days.[9]

Recommended Treatment Options

For adults with newly diagnosed active RA, NICE (National institute for Health and Care Excellence) recommends first line treatment with an oral csDMARD such as MTX, leflunomide or sulfasalazine within three months of the onset of persistent symptoms.[10] MTX is usually the first medicine given for RA, often with another csDMARD and a short course of steroids (corticosteroids) to relieve any pain.[10,11] These may be combined with biological treatments such as adalimumab, abatacept, etanercept, certolizumab pegol, golimumab, tocilizumab and infliximab which are also recommended for use after conventional DMARDs have failed. Other NICE recommended treatments for moderate to severe active RA include rituximab, baracitinib, tofacitinib, filgotinib, upadacitinib and sarilumab.[10-12]

Clinical Trial Information

Trial	**BAROQUE;** NCT02504671, 2014-003453-34; A Phase IIb, Double-Blind, Placebo-Controlled, Dose-Adaptive, Study of the Efficacy and Safety of GSK3196165 in Combination With Methotrexate Therapy, in Subjects With Active Moderate-Severe Rheumatoid Arthritis Despite Treatment With Methotrexate **Phase II** – Completed **Location(s):** 8 EU countries, UK, Canada and other countries **Study completion date:** December 2017
Trial Design	Randomised, parallel assignment, double-blind
Population	N= 222; patients with active moderate to severe rheumatoid arthritis despite treatment with methotrexate; aged 18 year and older
Intervention(s)	Subject will receive GSK3196165 (SC administration) weekly, then every other week) in combination with MTX (orally or SC injection; 15-25 mg/week) and folic acid (>=5 mg/week).
Comparator(s)	Subjects will receive placebo (SC injection; weekly, then every other week) in combination with MTX (15-25 mg/week) and folic acid (>=5 mg/week).
Outcome(s)	Primary outcome measures: • Percentage of participants who achieved disease activity score for 28 different joints with C-reactive protein value (DAS28[CRP]) remission (DAS28 <2.6) at week 24 [time frame: week 24] See trial record for full list of other outcomes.
Results (efficacy)	Between July 23, 2015, and Dec 29, 2017, 222 patients were randomly assigned (37 to each group). 86 (49%) of 175 escaped to otilimab 180 mg at week 12 and 57 (69%) of 83 at week 24. At week 24, the proportion of patients with DAS28-

	CRP <2·6 was two (5%) of 37 in the otilimab 22·5 mg group, six (16%) of 37 in the 45 mg group, seven (19%) of 37 in the 90 mg group, five (14%) of 37 in the 135 mg group, five (14%) of 37 in the 180 mg, and one (3%) of 37 in the placebo group. The largest difference was achieved with otilimab 90 mg (16·2%; odds ratio [OR] 8·39, 95% CI 0·98–72·14; p=0·053).[13]
Results (safety)	Adverse events were reported pre-escape in 19–24 (51–65%) patients and post escape in 10–17 (40–61%) patients across otilimab dose groups and in 18 (49%) of 37 and 22 (67%) of 33 in the placebo group. The most common adverse event was nasopharyngitis: 3–9 (8–24%) in otilimab groups and one (3%) in the placebo group pre-escape and 1–3 (4–10%) in otilimab groups and seven (21%) in the placebo group post escape. Pre-escape serious adverse events were foot fracture (otilimab 45 mg); arthralgia, myocardial infarction, dizziness (otilimab 90 mg); oesophageal spasm, acute pyelonephritis (otilimab 22·5 mg), and uterine leiomyoma (otilimab 135 mg). Post-escape serious adverse events were ankle fracture (placebo) and rheumatoid arthritis (otilimab 135 mg). There were no deaths or pulmonary events of clinical concern, and rates of serious infection were low.[13]

Clinical Trial Information

Trial	**contRAst-1;** NCT03980483, 2019-000797-39**;** A 52-week, Phase 3, Multicentre, Randomised, Double Blind, Efficacy and Safety Study Comparing GSK3196165 With Placebo and With Tofacitinib, in Combination With Methotrexate in Participants With Moderately to Severely Active Rheumatoid Arthritis Who Have **Phase III –** Active, not recruiting **Location(s):** 7 EU countries, UK, USA, Canada, and other countries **Primary completion date**: September 2021
Trial Design	Randomised, parallel assignment, double-blind
Population	N=1537; Patients with moderate to severe active rheumatoid arthritis who have an inadequate response to methotrexate
Intervention(s)	• GSK3196165 SC injection once weekly • Placebo (to tofacitinib) capsule twice daily • A stable oral dose of MTX weekly • ≥5mg/week folic acid
Comparator(s)	• Tofacitinib (capsule) • MTX (oral administration) • Folic acid • Placebo (to GSK3196165) administered by SC injection
Outcome(s)	Primary outcome measure: • Proportion of participants achieving 20% improvement in American College of Rheumatology Criteria (ACR20) at week 12: superiority comparison with placebo [time frame: week 12] See trial record for full list of other outcomes.

Results (efficacy)	-
Results (safety)	-

Trial	**contrRAst-2,** NCT03970837, A 52-week, Phase 3, Multicentre, Randomised, Double Blind, Efficacy and Safety Study, Comparing GSK3196165 With Placebo and With Tofacitinib in Combination With Conventional Synthetic DMARDs, in Participants With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Conventional Synthetic DMARDs or Biologic DMARDs **Phase III** – Active, not recruiting **Location(s):** 7 EU countries, UK, US and other countries **Primary completion date:** October 2021
Trial Design	Randomised, parallel assignment, double-blind
Population	N=1764; 18 years and older; RA (active disease); inadequate response to one or two conventional synthetic (csDMARDs) (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, bucillamine, or iguratimod) or biologic DMARDs.
Intervention(s)	• 90mg or 150mg GSK3196165 once weekly (SC injection) • Stable dose of csDMARDS as standard of care • Placebo to tofacitinib (capsule)
Comparator(s)	• Tofacitinib (capsule) • Stable dose of csDMARDS as standard of care • Placebo to GSK3196165 administered by SC injection
Outcome(s)	Primary outcome measure: Proportion of participants achieving 20% improvement in American College of Rheumatology Criteria (ACR20) at Week 12: superiority comparison with placebo [Time Frame: Week 12] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	**contrRAst-3,** NCT04134728; A 24-week, Phase 3, Multicentre, Randomised, Double-blind, Efficacy and Safety Study, Comparing GSK3196165 With Placebo and With Sarilumab, in Combination With Conventional Synthetic DMARDs, in Participants With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Biological DMARDs and/or Janus Kinase Inhibitors **Phase III** – Completed **Location(s):** 8 EU countries, UK, US, and other countries **Study completion date:** February 2022
Trial Design	Randomised, parallel assignment, double blind

Population	N=550; aged 18 years and older; RA (active disease); inadequate response to one or two conventional synthetic (csDMARDs) (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, bucillamine, or iguratimod) and an inadequate response to biological DMARDs and/or Janus Kinase Inhibitors
Intervention(s)	• 90mg or 150mg GSK3196165 once weekly (SC injection) • Stable dose of csDMARDS as standard of care
Comparator(s)	• Sarilumab (SC injection) • Placebo to GSK3196165 (SC injection) • Stable dose of csDMARDS as standard of care
Outcome(s)	Primary outcome measure: Proportion of participants achieving 20% improvement in American College of Rheumatology Criteria (ACR20) at Week 12: superiority comparison with placebo [Time Frame: Week 12] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	**contrast X;** NCT04333147, 2019-000878-30; A Multi-centre Long-term Extension Study to Assess the Safety and Efficacy of GSK3196165 in the Treatment of Rheumatoid Arthritis **Phase III –** Recruiting **Location(s):** 10 EU countries, UK, USA, Canada, and other countries **Primary completion date:** April 2024
Trial Design	Randomised, parallel assignment, double-blind,
Population	N= 3000 (planned); participants with moderate to severe active rheumatoid arthritis and have completed a previous qualifying study (NCT03980483, NCT03970837, or NCT04134728) or investigators think would benefit from extended treatment (NCT0433314); aged 18 years and older
Intervention(s)	GK3196165 (90 mg or 150 mg weekly, via SC injection) in addition to standard of care csDMARD treatment.
Comparator(s)	No active comparator
Outcome(s)	Primary outcome measures: • Incidence of AEs, SAEs and adverse events of special interests (AESI) [time frame: up to 4 years] • Change from baseline in platelet count, neutrophils lymphocytes, monocytes, eosinophils, and basophils (Giga cells per litre [giga cells/L]) [time frame: baseline (day 1) and up to 4 years] • Change from baseline in haemoglobin level (Grams per litre) [time frame: baseline (day 1) and up to 4 years]

	• Change from baseline in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein-cholesterol, triglycerides and other lipoprotein tests as needed (millimoles per litre) [time frame: baseline (day 1) and up to 4 years] • Change from Baseline in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP) gamma-glutamyl transferase (GGT) levels, lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) (International units per litre) [time frame: baseline (Day 1) and up to 4 years] • Change from Baseline in total and direct bilirubin (Micromoles per litre) [time frame: baseline (Day 1) and up to 4 years] • Change from Baseline in albumin level (Grams per litre) [time frame: baseline (Day 1) and up to 4 years] • Proportion of participants with National Cancer Institute-Common terminology criteria for adverse events (NCI-CTCAE) more than or equal to (>=) grade 3 haematological/clinical chemistry abnormalities [time frame: up to 4 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of otilimab 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. Tocilizumab 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. 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). October 2020.
- NICE quality standard. Rheumatoid arthritis in over 16s (QS33). January 2020.
- NICE diagnostic guidance. Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis (DG36). July 2019.

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. Guideline for the treatment of rheumatoid arthritis. 2021.[14]
- European Alliance of Associations for Rheumatology. Recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. 2019.[15]
- NHS Quality Improvement Scotland. Management of early rheumatoid arthritis: a national clinical guideline. 2011.[16]

Additional Information

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2 ClinicalTrials.gov. *Efficacy and Safety of GSK3196165 Versus Placebo and Tofacitinib in Participants With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate (contRAst 1). Trial ID: NCT03980483*. 2019. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03980483 [Accessed June 1st, 2022].

3 ClinicalTrials.gov. *Efficacy and Safety of GSK3196165 Versus Placebo and Tofacitinib in Participants With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Conventional Synthetic (cs)/Biologic (b) Disease Modifying Anti-rheumatic Drugs (DMARDs) (contRAst 2). Trial ID: NCT03970837*. 2019. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03970837 [Accessed July 5th, 2022].

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