Health Technology Briefing
March 2024

Depemokimab as adjunctive therapy for severe asthma with an eosinophilic phenotype in patients aged 12 years and older

Company/Developer	GlaxoSmithKline UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 31124	NICE ID: Not Available	UKPS ID: 667943

Licensing and Market Availability Plans

Currently in phase III/II trials.

Summary

Severe asthma is the most serious type of asthma where symptoms are hard to control, even with high doses of medicine. Severe asthma with an eosinophilic phenotype makes up approximately 50% of all severe asthmatic cases. It is characterised by tissue and sputum eosinophilia, which is when there are unusually high levels of eosinophils (a type of white blood cell) in the blood. Over the last 20 years, biological therapy for eosinophil diseases, including asthma, has improved. However, global treatment efficacy is still suboptimal. As novel therapies and biologic agents become available, there is an increased need for specific subtype-directed treatment strategies.

Depemokimab is currently in development to treat severe asthma with an eosinophilic phenotype and has been engineered for long-acting suppression of IL-5 function. IL-5 is a cell signalling protein that binds to its receptor to aid in eosinophil development and survival. Therefore, depemokimab reduces the number of eosinophils in the body by suppressing IL-5 activity. Depemokimab is more potent, has a longer half-life and a less frequent twice-yearly dosing schedule. It is administered subcutaneously (under the skin) from a pre-filled syringe. If licensed, depemokimab will offer an additional treatment option as adjunctive therapy for patients with severe asthma with an eosinophilic phenotype.

Proposed Indication

Adults and adolescent patients 12 years or older, with severe asthma with an eosinophilic phenotype.[1]

Technology

Description

Depemokimab (GSK3511294, GSK'294)[2] is a long-acting anti-IL-5 monoclonal antibody (mAb) currently in development for the treatment of severe asthma with an eosinophilic phenotype.[1,2] It blocks IL-5 from binding to its receptor.[3] IL-5 is the major cytokine responsible for the differentiation,[4] division, growth, activation and survival of eosinophils.[2] Eosinophils are one of several white blood cell types that support the immune system,[5] and high eosinophil numbers in airway sputum are a hallmark biomarker of T2 phenotypic asthma (asthma that is characterized by the build-up of type 2 immune cells such as eosinophils and mast cells in lung tissue.[6,7,8] Therefore, blocking IL-5 ultimately reduces the number of eosinophils in the body.[9] Depemokimab has also been engineered for long-acting suppression of IL-5 activity[2] and improved IL-5 affinity versus other anti-IL-5 mAbs.[10] It has a more potent pharmacology, a longer half-life and a less frequent, twice-yearly dosing schedule.[11]

Depemokimab is in development for adults and adolescents 12 years or older with severe asthma with an eosinophilic phenotype.[1] In the ongoing phase III trial NCT04718389, depemokimab is administered subcutaneously every 6 months[2] from a single-use prefilled syringe.[1]

Key Innovation

Severe asthma with an eosinophilic phenotype is a distinct phenotype of severe asthma with frequent exacerbations and poor prognosis.[12] High numbers of eosinophils can persist despite treatment with inhaled and oral corticosteroids, leading to severe refractory eosinophilic asthma.[13] During the last 20 years, biological therapy of eosinophil diseases, including asthma, has significantly improved.[14] However, the global treatment efficacy is still far from optimal.[14] As novel therapies and biologic agents become increasingly available, there is an increased need for specific subtype-directed treatment strategies.[15]

Most other IL-5 inhibitors are administered every 4 or 8 weeks, while depemokimab is to be administered every 6 months.[16] Such a long-lasting effect, allowing infrequent administration, would likely increase patient adherence to the therapy while lowering the risk of adverse reactions.[16] Depemokimab has been engineered for long-acting suppression of IL-5 activity[2] and improved IL-5 affinity versus other anti-IL-5 mAbs.[10] It has a more potent pharmacology, a longer half-life and twice-yearly dosing schedule.[11] Phase 1 clinical trial results of depemokimab among patients with severe asthma with an eosinophilic phenotype show depemokimab was well tolerated, with linear and dose-proportional effects such as blood eosinophil reductions and extended half-life supporting less frequent dosing versus other anti-IL-5 mAbs.[10] Reductions in blood eosinophil counts of 48% or more were also seen in the depemokimab group, but not in the placebo groups.[10] If licensed, depemokimab will offer an additional treatment as adjunctive[17] therapy option for patients with severe asthma with an eosinophilic phenotype.

Regulatory & Development Status

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

Depemokimab is currently in phase III clinical development for the following conditions:[18]

- Eosinophilic granulomatosis with polyangiitis
- Nasal polyps
- Hypereosinophilic syndrome
- Eosinophilic granulomatosis with polyangiitis

Patient Group

Disease Area and Clinical Need

Asthma is a common lung condition that causes occasional breathing difficulties. People with asthma have inflamed and "sensitive" airways that become narrow and clogged with sticky mucus in response to certain triggers.[19] It affects people of all ages and normally starts in childhood, although it can also develop for the first time in adults.[20] Severe asthma is the most serious and life-threatening type of asthma where symptoms are harder to control, even with high doses of medicine.[21] One of the severe asthma phenotypes is severe asthma with an eosinophilic phenotype, which is characterized by eosinophilia in sputum/blood driven by type 2 immune responses.[22] This severe asthma phenotype is found in approximately 50% of people with severe asthma. [23] It is characterized by frequent exacerbations and a poor prognosis.[12] Although a standard definition has not been developed yet, peripheral blood eosinophil counts ranging from ≥150 cells/microlitre to ≥400 cells/microlitre have been used to define eosinophilic asthma.[24] Normal absolute eosinophil count ranges from 0 to 500 cells per microliter, insinuating that eosinophilic asthmas can have an eosinophil count within the normal range.[25] The main symptoms of asthma are wheezing, breathlessness, a tight chest and coughing, which can temporarily worsen when an asthma attack happens.[20] Genetics, pollution and modern hygiene standards have been suggested as causes, but there is not currently enough evidence to confirm these as causal mechanisms.[19] Risk factors for asthma include having an allergy-related condition such as eczema, a food allergy or having family history of these conditions, exposure to tobacco smoke or having a mother who smoked during pregnancy.[19]

In the UK, 5.4. million people have asthma.[26] Approximately 160,000 people in the UK are diagnosed with asthma each year, however, incidence rates went down by around 10% between 2008 and 2012.[27] Around 200,000 people in the UK have severe asthma, meaning that out of every 100 people with asthma in the UK, around four have severe asthma.[21] Based on prevalence estimates, 50% of these could be cases of severe asthma with an eosinophilic phenotype (type 2 inflammation).[23] In England in 2022-23, there were 81,828 finished consultant episodes (FCE) and 56,853 admissions for a primary diagnosis of asthma (ICD-10 code J45), of which severe asthma makes up 4% of cases, which resulted in 125,908 FCE bed days and 8,703 day cases.[28]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following treatment options for severe asthma and severe asthma with type 2 inflammation respectively :[29,30]

- Tezepelumab
- Dupilumab

Clinical Trial Information I

Trial	**SWIFT-2;** NCT04718103, EudraCT-2020-003611-10; A 52-week, Randomised, Double-blind, Placebo-controlled, Parallel-group, Multi-centre Study of the Efficacy and Safety of GSK3511294 Adjunctive Therapy in Adult and Adolescent Participants With Severe Uncontrolled Asthma With an Eosinophilic Phenotype **Phase III** – ongoing **Location(s)** Six EU countries, USA, Canada and other countries **Primary completion date**: April 2024
Trial Design	Randomised, double-blind, placebo-controlled, parallel group

Population	N = 397 (Actual); participants with severe uncontrolled asthma with an eosinophilic phenotype; aged 12 years or older
Intervention(s)	Depemokimab in a pre-filled syringe
Comparator(s)	Matched placebo
Outcome(s)	Annualized rate of clinically significant exacerbations over 52 weeks. See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information II	
Trial	**SWIFT-1;** NCT04719832, EudraCT-2020-003632-25; A 52-week, Randomised, Double-blind, Placebo-controlled, Parallel-group, Multi-centre Study of the Efficacy and Safety of GSK3511294 Adjunctive Therapy in Adult and Adolescent Participants With Severe Uncontrolled Asthma With an Eosinophilic Phenotype **Phase III** – ongoing **Location(s)** Seven EU countries, UK, USA, Canada and other countries **Primary completion date**: Nov 2023
Trial Design	Randomised, double-blind, placebo-controlled, parallel-group
Population	N = 395 (actual); participants with severe uncontrolled asthma with an eosinophilic phenotype; aged 12 years or older
Intervention(s)	Depemokimab administered using a pre-filled syringe
Comparator(s)	Matched placebo
Outcome(s)	Annualized rate of clinically significant exacerbations over 52 weeks. See trial record for a full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information III	
Trial	**NIMBLE;** NCT04718389, EudraCT 2020-003612-28; A 52-week, Randomised, Double-blind, Double-dummy, Parallel Group, Multi-centre, Non-inferiority Study Assessing Exacerbation Rate, Additional Measures of Asthma Control and Safety in Adult and Adolescent Severe Asthmatic Participants With an Eosinophilic Phenotype Treated With GSK3511294 Compared With Mepolizumab or Benralizumab. **Phase III** – recruiting

	Location(s): 12 EU countries, UK, USA, Canada and other countries **Primary completion date** – July 2025
Trial Design	Randomised, parallel assignment, double-blind
Population	N = 1700 (planned); patients with severe asthma with an eosinophilic phenotype; aged 12 years or older.
Intervention(s)	Depemokimab in single-use prefilled syringe
Comparator(s)	Participant's anti-IL-5/5R treatment prior to randomization (either mepolizumab or benralizumab), plus matching placebo
Outcome(s)	Primary outcome: annualized rate of clinically significant exacerbations over 52 weeks. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information IV	
Trial	**AGILE**; NCT05243680, EudraCT-2020-004334-38; A Multi-centre, Single Arm, Open-label Extension Study to Evaluate the Long-term Safety of GSK3511294 (Depemokimab) in Adult and Adolescent Participants With Severe Asthma With an Eosinophilic Phenotype From Studies 206713 or 213744 **Phase III** – ongoing **Location(s)** Seven EU countries, UK, USA, Canada and other countries **Primary completion date**: May 2025
Trial Design	Single group assignment, open label
Population	N = 637 (estimated); participants who completed the double-blind intervention treatment during Study 206713 (NCT04719832) or Study 213744 (NCT04718103)
Intervention(s)	Depemokimab administered as pre-filled syringe
Comparator(s)	Not applicable
Outcome(s)	Number of participants with adverse events (AEs) and serious adverse events (SAEs) over 52 weeks. See trial record for full list other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of depemokimab is not yet known.

Relevant Guidance

NICE Guidance

- NICE Technology appraisal. Tezepelumab for treating severe asthma (TA880). April 2023.
- NICE Technology appraisal. Dupilumab for treating severe asthma with type 2 inflammation (TA751). December 2021.
- NICE guideline. Asthma: diagnosis, monitoring and chronic asthma management (NG80). November 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Paediatric Medicines: Respiratory. E03/S/g.

Other Guidance

- European Respiratory Society (ERS). European Respiratory Society Guidelines for the Diagnosis of Asthma in Adults. 2022.[31]
- ERS & American Thoracic Society (ATS). Management of severe asthma: a ERS/ATS guideline. 2020.[32]
- Scottish Intercollegiate Guidelines Network (SIGN) and British Thoracic Society (BTS). British guideline on the management of asthma. 2019.[33]
- ERS & ATS. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. 2014.[34]

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