NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
March 2024

Budesonide-glycopyrronium-formoterol fumarate for the treatment of severe and inadequately controlled asthma

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30687	NICE TSID: Not available	UKPS ID: 673121

Licensing and Market Availability Plans

Phase III clinical trial ongoing

Summary

Budesonide-glycopyrronium-formoterol fumarate is in development for the treatment of severe asthma. Asthma is a common lung condition that causes occasional breathing difficulties. It affects people of all ages and often starts in childhood, although it can also develop for the first time in adults. Asthma is caused by swelling (inflammation) of the breathing tubes that carry air in and out of the lungs. This makes the tubes highly sensitive, so they temporarily narrow. It may happen randomly or after exposure to a trigger. Common asthma triggers include allergies, smoke, pollution and cold air, exercise, and infections like colds or flu. Severe asthma is asthma that does not respond well to regular asthma treatment. The main symptoms of asthma include breathlessness, coughing, wheezing, and a tight chest, and these symptoms can sometimes get temporarily worse (asthma attack).

Budesonide-glycopyrronium-formoterol fumarate is a triple fixed-dose combination therapy administered via inhalation, where the combination is expected to work together to improve severe asthma treatment by widening the airways and improving breathing. If licenced, budesonide-glycopyrronium-formoterol fumarate may provide a new combination treatment option for patients aged 12 to 80 years with severe and inadequately controlled asthma.

Proposed Indication

Treatment of adult and adolescent patients with severe asthma inadequately controlled with standard care.[1,2]

Technology

Description

Budesonide-glycopyrronium-formoterol fumarate is a triple fixed-dose combination metered dose inhaler formulated with budesonide, glycopyrronium and formoterol fumarate dihydrate. This provides a combination of an inhaled corticosteroid (ICS), long-acting muscarinic antagonist (LAMA), and long-acting β2-agonist (LABA) in one single inhaler.[3] Budesonide, an ICS, suppresses airway inflammation leading to reduced bronchial hyperresponsiveness. Formoterol fumarate, a LABA, acts on bronchial smooth muscle β adrenoceptors and causes bronchodilation.[4] Glycopyrronium, a LAMA, targets muscarinic receptors located in the respiratory tract. It exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation.[5]

Budesonide-glycopyrronium-formoterol fumarate is currently in development for the treatment of patients aged 12 to 80 years with severe and inadequately controlled asthma. In phase III clinical trials (KALOS, NCT04609878 and LOGOS, NCT04609904), participants will receive 320/28.8/9.6 µg and 320/14.4/9.6 µg of budesonide-glycopyrronium-formoterol fumarate metered dose inhaler.[1,2]

Key Innovation

Despite the availability of effective inhaled therapies, many patients with asthma have poor asthma control. Uncontrolled asthma presents a significant burden on the patient and society, and, for many, remains largely preventable.[6] Satisfactory asthma control still remains an unmet need worldwide.[7] A pilot study that evaluated budesonide-glycopyrronium-formoterol fumarate triple therapy in patients with asthma-chronic obstructive pulmonary disease overlap (asthma-COPD overlap), resulted in an improvement in lung function parameters including inspiratory capacity.[8] Growing evidence is documenting the importance of using the triple combination of ICS, long-acting β2-agonist (LABA), and long-acting muscarinic antagonist (LAMA) in the treatment of asthma.[9] If licenced, budesonide-glycopyrronium-formoterol fumarate is expected to provide a new combination treatment option for patients with severe and inadequately controlled asthma.

Regulatory & Development Status

Budesonide-glycopyrronium-formoterol fumarate has Marketing Authorisation in the EU/UK for maintenance treatment of moderate-to-severe COPD.[10]

Budesonide-glycopyrronium-formoterol fumarate is also currently in phase II/III development for the treatment of Chronic Obstructive Pulmonary Disease (COPD).[11]

Patient Group

Disease Area and Clinical Need

Asthma is a common lung condition that causes occasional breathing difficulties. It affects people of all ages and often starts in childhood, although it can also develop for the first time in adults.[12] Severe asthma,

as defined by the European Respiratory Society/American Thoracic Society, is an asthma that requires treatment with high-dose inhaled ICS plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.[13] About 4% of people with asthma have what is known as severe asthma.[14] Asthma is caused by inflammation of the breathing tubes that carry air in and out of the lungs. This makes the tubes highly sensitive, so they temporarily narrow. It may happen randomly or after exposure to a trigger. Common asthma triggers include allergies (to house dust mites, animal fur or pollen, for example), smoke, pollution, cold air, exercise, and infections like colds or flu. The main symptoms of asthma include breathlessness, coughing, wheezing, and a tight chest, and these symptoms can sometimes get temporarily worse. This is known as an asthma attack.[12]

Asthma affects more than 300 million people worldwide including 11.6% of children aged 6 to 7 years. In the UK, over 8 million people, or approximately 12% of the population, have been diagnosed with asthma. However, some may have grown out of the condition, and 5.4 million people are receiving asthma treatment.[15] In England (2022-23) there were 81,828 finished consultant episodes (FCEs) and 56,853 admissions for asthma (ICD-10 code J45), which resulted in 8,703 day cases and 125,908 FCE bed days.[16]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following for the treatment of severe asthma.[17-19]

- Tezepelumab
- Tiotropium
- Theophylline

Clinical Trial Information

Trial	**KALOS**; NCT04609878, EudraCT 2020-001520-34; A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicenter Variable Length Study to Assess the Efficacy and Safety of PT010 Relative to PT009 and Symbicort in Adult and Adolescent Participants With Inadequately Controlled Asthma **Phase III** – Recruiting **Location(s):** Nine EU countries, Australia, Canada, US and others **Primary Completion Date:** March 2025
Trial Design	Randomised, parallel assignment, quadruple masking, active comparator-controlled
Population	N=2,200 (estimated); individuals aged 12 to 80 years, with BMI less than 40kg/m^2, who have a one-year and above documented history of physician-diagnosed asthma
Intervention(s)	Budesonide-glycopyrronium-formoterol fumarate metered dose inhalers (BGF MDI 320/28.8/9.6 µg & BGF MDI 320/14.4/9.6 µg)
Comparator(s)	Budesonide-formoterol fumarate (BFF) MDI 320/9.6 µg and budesonide-formoterol fumarate pressurized metered dose inhaler (pMDI) 320/9 µg
Outcome(s)	Primary outcome measures: - Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve 0 to 3 hours (AUC0-3) at Week 24 [Time frame: 24 weeks]

	- Rate of severe asthma exacerbations [Time frame: up to 52 weeks] See the trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**LOGOS**; NCT04609904, EudraCT 2020-001521-31; A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicenter Variable Length Study to Assess the Efficacy and Safety of PT010 Relative to PT009 and Symbicort® in Adult and Adolescent Participants With Inadequately Controlled Asthma **Phase III** – Recruiting **Location(s):** Seven EU countries, UK, US, and others **Primary Completion Date:** March 2025
Trial Design	Randomised, parallel assignment, quadruple masking, active comparator-controlled
Population	N=2,200 (estimated); individuals aged 12 to 80 years, with BMI less than 40kg/m^2, who have a one-year and above documented history of physician-diagnosed asthma
Intervention(s)	Budesonide-glycopyrronium-formoterol fumarate metered dose inhalers (BGF MDI 320/28.8/9.6 µg & BGF MDI 320/14.4/9.6 µg)
Comparator(s)	Budesonide-formoterol fumarate (BFF) MDI 320/9.6 µg and budesonide-formoterol fumarate pressurized metered dose inhaler (pMDI) 320/9 µg
Outcome(s)	Primary outcome measures: - Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve 0 to 3 hours (AUC0-3) at Week 24 [Time frame: 24 weeks] - Rate of severe asthma exacerbations [Time frame: up to 52 weeks] See the trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Budesonide-glycopyrronium-formoterol fumarate inhaler is already marketed in the UK; one unit of budesonide-glycopyrronium-formoterol fumarate costs £44.50 according to the National Health Service (NHS) indicative price.[20]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Asthma: diagnosis, monitoring and chronic asthma management (GID-NG10186). October 2024
- NICE technology appraisal guidance. Tezepelumab for treating severe asthma (TA880). April 2023.
- NICE guideline. Asthma: diagnosis, monitoring and chronic asthma management (NG80). November 2017. Last updated: March 2021.
- NICE quality standard. Asthma (QS25). February 2013. Last updated: September 2018.
- NICE interventional procedure guidance. Bronchial thermoplasty for severe asthma (IPG635). December 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. Specialised Respiratory Services (adult) – Severe Asthma. 170002/S. 2017.

Other Guidance

- Royal Cornwall Hospitals NHS Trust. Acute Exacerbation of Asthma in Adults Clinical Guideline V3.0. 2022.[21]
- University Hospitals of Leicester NHS trust, Nottingham University Hospitals NHS Trust, and the Children's Medical Emergency Transport (COMET). Acute severe asthma - Guidelines for management. 2020.[22]
- Holguin F, Cardet JC, Chung KF, *et al*. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. 2020.[23]
- Pan-Birmingham Respiratory Clinical Network and Birmingham, Solihull, Sandwell, and Environs Area Prescribing Committee (BSSE APC). Diagnosis and Management of Asthma in Adults: APC Guideline Diagnosis and Management of Asthma in Adults. 2019.[24]
- Health Improvement Scotland and the Scottish Intercollegiate Guidelines Network (SIGN). British guideline on the management of asthma: A national clinical guideline (SIGN 158). 2019.[25]

Additional Information

AstraZeneca UK Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision-making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 ClinicalTrials.gov. *Study to Assess PT010 in Adult and Adolescent Participants With Inadequately Controlled Asthma (KALOS) (KALOS). Trial ID: NCT04609878*. 2020. Status: Recruiting. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04609878? [Accessed 03 October, 2023].

2 ClinicalTrials.gov. *Study to Assess PT010 in Adult and Adolescent Participants With Inadequately Controlled Asthma (LOGOS) (LOGOS). Trial ID: NCT04609904*. 2020. Status: Recruiting. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04609904? [Accessed 03 October, 2023].

3 Dorinsky P, DePetrillo P, Siddiqui S, Maes A, Reisner C. Safety and pharmacokinetics of budesonide/glycopyrronium/formoterol fumarate dihydrate metered dose inhaler (BGF MDI) in healthy adult subjects of Japanese descent. *Pulmonary Pharmacology and Therapeutics*. 2018;51:18-25. Available from: https://doi.org/https://doi.org/10.1016/j.pupt.2018.05.001.

4 O'Carroll O, McCarthy C, Butler MW. Treatments for poorly controlled asthma. *BMJ*. 2021;375:n2355. Available from: https://doi.org/10.1136/bmj.n2355.

5 European Medicines Agency (EMA). *Trixeo Aerosphere*. 2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/trixeo-aerosphere [Accessed 27 October 2023].

6 Busse WW, Kraft M. Current unmet needs and potential solutions to uncontrolled asthma. *European Respiratory Review*. 2022;31(163):210176. Available from: https://doi.org/10.1183/16000617.0176-2021.

7 Caminati M, Vaia R, Furci F, Guarnieri G, Senna G. Uncontrolled Asthma: Unmet Needs in the Management of Patients. *Journal of Asthma and Allergy*. 2021;Volume 14:457-66. Available from: https://doi.org/10.2147/jaa.s260604.

8 Ishiura Y, Fujimura M, Ohkura N, Hara J, Kasahara K, Ishii N, et al. Triple Therapy with Budesonide/Glycopyrrolate/Formoterol Fumarate Improves Inspiratory Capacity in Patients with Asthma-Chronic Obstructive Pulmonary Disease Overlap. *International Journal of Chronic Obstructive Pulmonary Disease*. 2020;15:269-77. Available from: https://doi.org/10.2147/copd.s231004.

9 Cazzola M, Braido F, Calzetta L, Matera MG, Piraino A, Rogliani P, et al. The 5T approach in asthma: Triple Therapy Targeting Treatable Traits. *Respiratory Medicine*. 2022;200:106915. Available from: https://doi.org/https://doi.org/10.1016/j.rmed.2022.106915.

10 National Institute for Health and Care Excellence (NICE): British National Formulary (BNF). *Formoterol fumarate with glycopyrronium and budesonide*. 2023. Available from: https://bnf.nice.org.uk/drugs/formoterol-fumarate-with-glycopyrronium-and-budesonide/ [Accessed 19 October 2023].

11 ClinicalTrials.gov. *Budesonide/glycopyrronium/formoterol fumarate | Phase 2, 3*. *Trial ID: https://classic.clinicaltrials.gov/ct2/results?term=Budesonide%2Fglycopyrronium%2Fformoterol+fumarate&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply*. 2024.[Accessed 18 March 2024].

12 National health Service (NHS). *Asthma*. 2021. Available from: https://www.nhs.uk/conditions/asthma/ [Accessed 18 October 2023].

13 Jackson DJ, Busby J, Pfeffer PE, Menzies-Gow A, Brown T, Gore R, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. *Thorax*. 2021;76(3):220-7. Available from: https://doi.org/10.1136/thoraxjnl-2020-215168.

14 Asthma and Lung UK. *Types of asthma*. 2022. Available from: https://www.asthmaandlung.org.uk/conditions/asthma/types-asthma [Accessed 18 October 2023].

15 National Institute for Health and Care Excellence (NICE). *Asthma: What is the prevalence of asthma?* 2023. Available from: https://cks.nice.org.uk/topics/asthma/background-information/prevalence/ [Accessed 18 October 2023].

16 National Health Service (NHS) 75 Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2F34%2FC4E943%2Fhosp-epis-stat-admi-diag-2022-23-tab.xlsx&wdOrigin=BROWSELINK [Accessed 19 March 2024].

17 National Institute for Health and Care Excellence (NICE). *Tezepelumab for treating severe asthma*. 2023. Available from: https://www.nice.org.uk/guidance/TA880/chapter/1-recommendations [Accessed 18 October 2023].

18 National Institute for Health and Care Excellence (NICE): British National Formulary (BNF). *Theophylline*. 2023. Available from: https://bnf.nice.org.uk/drugs/theophylline/#side-effects [Accessed 19 October 2023].

19 National Institute for Health and Care Excellence (NICE): British National Formulary (BNF). *Tiotropium*. 2023. Available from: https://bnf.nice.org.uk/drugs/tiotropium/#indications-and-dose [Accessed 19 October 2023].

20 National Institute for Health and Care Excellence (NICE): British National Formulary (BNF). *Formoterol fumarate with glycopyrronium and budesonide: Medicinal forms*. 2023. Available from: https://bnf.nice.org.uk/drugs/formoterol-fumarate-with-glycopyrronium-and-budesonide/medicinal-forms/ [Accessed 03 October, 2023].

21 Royal Cornwall Hospital NHS Trust. *Acute Exacerbation of Asthma in Adults Clinical Guideline V3.0*. 2022. Available from: https://doclibrary-rcht.cornwall.nhs.uk/DocumentsLibrary/RoyalCornwallHospitalsTrust/Clinical/Respiratory/AcuteExacerbationsOfAsthmaInAdultsClinicalGuideline.pdf [Accessed 19 October 2023].

22 University Hospitals of Leicester NHS Trust, Nottingham University Hospitals NHS Trust, and the Children's Medical Emergency Transport (CoMET). *Acute severe asthma - Guidelines for management*. 2020. Available from: https://secure.library.leicestershospitals.nhs.uk/PAGL/Shared%20Documents/Acute%20Severe%20Asthma%20Management%20CoMET%20Guideline.pdf [Accessed 19 october 2023].

23 Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *European Respiratory Journal*. 2020;55(1):1900588. Available from: https://doi.org/10.1183/13993003.00588-2019.

24 Pan-Birmingham Respiratory Clinical Network, and Birmingham S, Sandwell and Environs Area Prescribing Committee (BSSE APC). *Diagnosis and Management of Asthma in Adults: APC Guideline Diagnosis and Management of Asthma in Adults*. 2019. Available from: https://www.birminghamandsurroundsformulary.nhs.uk/docs/acg/Diagnosis%20and%20Management%20of%20Asthma%20Guidelines.pdf?uid=193304120&uid2=201971101545289#:~:text=Acute%20Severe%20Asthma%20should%20be%20treated%20in%20accordance,and%20should%20include%20the%20items%20at%20point%203. [Accessed 19 October 2023].

25 Health Improvement Scotland and the Scottish Intercollegiate Guidelines Network (SIGN). *British guideline on the management of asthma: A national clinical guideline (SIGN 158).* 2019. Available from: https://www.sign.ac.uk/media/1773/sign158-updated.pdf [Accessed 19 October 2023].

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