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HEALTH TECHNOLOGY BRIEFING
MAY 2021

Dupilumab in addition to controller medications for children aged 6 to 11 years with asthma

NIHRIO ID	24119	**NICE ID**	10085
Developer/Company	Sanofi	**UKPS ID**	650401

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Dupilumab is in clinical development as an add-on to controller medications for the maintenance treatment in children aged 6 to <12 years with uncontrolled, moderate-to-severe asthma. Asthma is a common lung condition that causes wheezing, coughing and breathlessness. Individuals with asthma can suffer an asthma attack, which in severe cases can be fatal. Patients with severe asthma have ongoing daily symptoms despite high-intensity asthma treatment. Therefore, there is need for additional treatment strategies which includes a need for biological therapies.

Dupilumab is a targeted biological therapy that is taken subcutaneously. It acts by blocking certain proteins called interleukin-4 (IL-4) and interleukin-13 (IL-13) and mediates the pathways involved in the inflammatory process in asthma. If licensed, dupilumab will offer an additional add-on maintenance treatment option for children aged ≥ 6 to < 12 years with moderate-to-severe asthma that is uncontrolled on current treatment.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

An add-on maintenance treatment children aged 6 to <12 years with uncontrolled, moderate-to-severe asthma.[1,2]

TECHNOLOGY

DESCRIPTION

Dupilumab (Dupixent, SAR231893, REGN668) is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that inhibits IL-4 & IL-13 signalling. Dupilumab binds to the IL-4 receptor alpha chain (IL-4Rα), therefore inhibiting IL-4 signalling via the type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the type II receptor (IL-4Rα/IL-13Rα).[3] IL-4 and IL-13 are cytokines central to the pathogenesis of type 2 inflammation and atopic disease and primarily produced by T helper 2 (Th2) cells. IL-13 is thought to function as a primary disease-inducing effector cytokine, whereas IL-4 functions as a key amplifier of type 2 immunity by facilitating expansion of the $CD4^+$ Th2-cell population in secondary lymphoid organs.[4] Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.[3]

In a phase III clinical trial (NCT02948959) patients received 200 mg of dupilumab (in 1.14 mL for >30 kilograms bodyweight [BW]) or 100 mg (in 0.67 mL for less than or equal to (<=) 30 kg BW), via subcutaneous injection every two weeks for 52 weeks in combination with stable-dose background therapy of medium dose ICS with a second controller medication or high-dose ICS alone or high-dose ICS with second controller medication.[1,5]

INNOVATION AND/OR ADVANTAGES

Despite effective treatments being widely available and the existence of treatment guidelines, a significant population of severe asthma cases remain ineligible for these treatments or uncontrolled despite these treatments. In approximately 50% of these patients, there is strong evidence of the pathogenic role of Th2 cytokines, such as IL-4 and IL-13, orchestrating the eosinophilic and allergic inflammatory processes. Dupilumab has the ability to inhibit the biological effects of both IL-4 and IL-13.[6]

Studies have shown that dupilumab improves lung function and reduces the estimated exacerbation rate in patients with persistent asthma insufficiently controlled with medium-to-high doses of inhaled corticosteroids plus a long-acting beta agonist (LABA).[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Dupilumab is currently licensed in the UK for:[3]

- moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older old who are candidates for systemic therapy
- severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy
- add-on maintenance treatment for severe asthma in adults and adolescents 12 years and older with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment
- add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

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The most common adverse reactions with dupilumab are injection site reactions.[3]

Besides asthma treatment, dupilumab is currently in phase III clinical development for the treatment of the following conditions:[7]

- Allergic Fungal Rhinosinusitis
- Chronic Obstructive Pulmonary Disease
- Cold Urticaria
- Chronic Spontaneous Urticaria
- Neurodermatitis
- Allergic Bronchopulmonary Aspergillosis
- Bullous Pemphigoid
- Eosinophilic Esophagitis

Dupilumab is in phase II clinical development for the treatment of the following conditions:[8]

- Peanut Allergy
- Allergic Rhinitis
- Hand Eczema

PATIENT GROUP

DISEASE BACKGROUND

Asthma is a common lung condition that causes occasional breathing difficulties. Symptoms include wheezing, breathlessness, a tight chest and coughing.[9] Many things can cause these symptoms, but they are more likely to be caused by asthma if they: happen often and keep coming back; are worse at night and early in the morning; seem to happen in response to an asthma trigger (cold and flu, exercise, allergy, smoke, medicines, emotions, weather, mould or damp etc.).[10,11]

Asthma symptoms can get temporarily worse; this is known as an asthma attack or an exacerbation. Signs of a severe asthma attack include wheezing; coughing; chest tightness becoming severe and constant; breathlessness; breathing faster; fast heartrate; drowsiness, confusion, exhaustion, or dizziness; blue lips or fingers; and fainting.[10]

Despite the recent advances in diagnostic and therapeutic strategies, asthma still poses a substantial health and socioeconomic burden, in particular in its uncontrolled and severe forms. Severe asthma in children is characterised by sustained symptoms despite treatment with high doses of inhaled corticosteroids (ICS) or oral corticosteroids, and represents approximately 2–5% of childhood asthma cases.[12]

The exact cause of asthma is unknown. People with asthma have swollen and sensitive airways that become narrow and clogged with sticky mucus in response to certain triggers. Genetics, pollution, and modern hygiene standards have been suggested as causes, but there is not currently enough evidence to know if any of these do cause asthma. Risk factors associated with asthma are: having an allergy related condition (eczema, food allergy, hay fever); having a family history of asthma or atopic conditions; having had bronchiolitis; exposure to tobacco smoke as a child; mother smoking during pregnancy and being born prematurely (before 37 weeks) or with a low birth weight.[11]

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CLINICAL NEED AND BURDEN OF DISEASE

In England, 4.5 million people are currently receiving treatment for asthma including 932,000 children.[13] It is estimated that severe asthma affects <5% of people with asthma, this is a debilitating form of the condition that does not respond to usual treatments.[14] This would equate to around 46,600 children in England.[13]

In 2010-11, school absenteeism for asthma or asthma symptoms accounted for 252.4 days/1,000 children (95% CI, 241.3–263.5; n/N = 1,267/5,352), equivalent to 2.8 million (95 % CI, 2.6–3.0) absences.[15]

In England in 2019/20 there were 252,917 finished consultant episodes (FCE) with a primary diagnosis of asthma (ICD-10 code J45), of which 14,807 FCEs were for patients aged 5 to 14.[16]

Every 10 seconds, someone is having a potentially life-threatening asthma attack in the UK. On average, three people die from an asthma attack in the UK every day.[13] In England in 2019, there were 1,156 deaths with asthma (ICD-10 codes J45) recorded as the underlying cause, 7 of which were patients aged 5 to 14.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is no cure for asthma, therefore treatment aims to control symptoms so that asthma patients are able to have normal functionality whilst minimising adverse reactions to the treatment. Patients normally complete a personal action plan with their doctor or specialist asthma nurse. The personal action plan focusses on which medicines to take and adherence to regime, how to identify if asthma symptoms are getting worse and what to do if an acute asthma exacerbation occurs.[18]

Current guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment aligned with the pathway of Global Initiatives of Asthma (GINA).[19] If asthma symptoms are not under control, then the treatment should be increased to the next step. If asthma symptoms are under control, then treatment should be stepped down until the patient reaches a point where their asthma is under control at the lowest possible controlling therapy.[20]

Children that do not seem to respond to standard treatment are referred to as severe or difficult to control asthma, and these children experience substantial morbidity from asthma symptoms. Children with persistent symptoms and exacerbations despite correct inhaler technique and good medical adherence to standard asthma therapy (steroid-resistant or therapy resistant asthma) should be referred to an asthma specialist to consider add-on biologic therapies.[21,22]

CURRENT TREATMENT OPTIONS

Pharmacological treatment pathway for children and young people aged 5 to 16 children with newly diagnosed asthma or asthma that is uncontrolled on their current treatment:[23]

- short-acting beta$_2$ agonist (SABA) reliever therapy alone
- paediatric low dose of an ICS as the first-line maintenance therapy
- leukotriene receptor antagonist (LTRA) in addition to the ICS

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- LABA in combination with the ICS
- Maintenance and reliever therapy (MART) is a form of combined ICS and LABA treatment in which a single inhaler, containing both ICS and a fast-acting LABA, is used for both daily maintenance therapy and the relief of symptoms as required.
- The National Institute for Health and Care Excellence (NICE) recommends omalizumab for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year).[24,25]
- Mepolizumab is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older.[24,26]

PLACE OF TECHNOLOGY

If licenced, dupilumab will provide an additional add-on maintenance treatment in children 6 to <12 years of age with uncontrolled, moderate-to-severe asthma.

CLINICAL TRIAL INFORMATION

Trial	**VOYAGE; EFC14153,** NCT02948959, 2016-001607-23; A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Children 6 to <12 Years of Age With Uncontrolled Persistent Asthma **Phase III** - Completed **Location(s):** EU countries (not inc UK), Canada and the United States **Study completion date:** August 2020
Trial design	Randomised, parallel assignment, double-blinded
Population	N = 407 (actual), children 6 to <12 years of age, with a physician diagnosis of persistent asthma for ≥12 months prior to screening, existing background therapy of medium-dose inhaled corticosteroids with second controller medication or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months with a stable dose ≥1 month prior to screening.
Intervention(s)	Dupilumab 200 mg (in 1.14 mL for >30 kg BW) or 100 mg (in 0.67 mL for <= 30 kg BW), will be administered subcutaneously every 2 weeks added to current controller medications
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome; - Annualized rate of severe exacerbation events during the placebo-controlled treatment period [Time Frame: Baseline, Week 52] See trial record for full list of other outcomes.
Results (efficacy)	Of 408 patients randomized, 350 had a type 2 inflammatory asthma phenotype; 259 had blood eosinophils ≥300cells/µL at baseline. In patients with a type 2 phenotype, dupilumab reduced the exacerbation rate by 59.3% (P<0.0001), and improved FEV_1pp (least squares [LS] mean difference vs placebo 5.21%; P=0.0009) and reduced FeNO levels (LS

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	mean difference vs placebo −17.84ppb; *P*<0.0001) at Week 12 compared with placebo. At Week 24, dupilumab showed greater improvement in Asthma Control Questionnaire-Interviewer Administered (ACQ-7-IA) scores from baseline vs placebo (LS mean difference vs placebo −0.33, *P*=0.0001). Similar findings were observed in patients with eosinophils ≥300cells/µL.[2]
Results (safety)	In the safety population, overall rates of treatment-emergent adverse events (TEAEs) in dupilumab vs placebo groups were 83% vs 80%. 13/271 (4.8%) dupilumab-treated patients and 6/134 (4.5%) placebo-treated patients reported serious TEAEs; 5/271 (1.8%) dupilumab-treated and 2/134 (1.5%) placebo-treated patients reported AEs leading to permanent study discontinuation.[2]

Trial	**Liberty Asthma Excursion;** NCT03560466, 2017-003317-25; One Year Study to Evaluate the Long-term Safety and Tolerability of Dupilumab in Pediatric Patients With Asthma Who Participated in a Previous Dupilumab Asthma Clinical Study **Phase III** – active, not recruiting **Location(s):** EU countries (not inc UK), Canada and the United States **Primary completion date**: October 2023
Trial design	Open label, single group assignment
Population	N = 354 (estimated), children 7 to 12 years of age, paediatric patients with asthma who completed the treatment in a dupilumab asthma trial (EFC14153).
Intervention(s)	Doses of dupilumab administered every 2 weeks or every 4 weeks added to current controller medications for 52 weeks.
Comparator(s)	None
Outcome(s)	Primary outcome; - Treatment-emergent adverse events (TEAEs) [Time Frame: From Day 1 up to Week 64] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Dupilumab is already marketed in the UK for the treatment of moderate to severe atopic dermatitis; two pre-filled disposable injections (150 mg/1 ml) cost £1,264.89.[27]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Mepolizumab for treating severe eosinophilic asthma (TA671). February 2021.

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- NICE technology appraisal guidance. Omalizumab for treating severe persistent allergic asthma (TA278). April 2013.
- NICE technology appraisal guidance. Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years (TA131). November 2007.
- 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.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN). British Guidelines on the Management of Asthma. 2016.[19]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Children 6 to <12 Years of Age With Uncontrolled Persistent Asthma. *Trial ID: NCT02948959*. 2016;Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT02948959.

2 L. B. Bacharier JFM, C. H. Katelaris, A. G. Fiocchi, R. Gagnon, I. de Mir, N. Jain, L. D. Sher, X. Mao, D. Liu, Y. Zhang, A. H. Khan, U. Kapoor, F. A. Khokhar, P. Rowe, Y. Deniz, M. Ruddy, E. Laws, N. Amin, L. P. Mannent, D. J. Lederer, M. Hardin. A1204 - Dupilumab Efficacy and Safety in Children with Uncontrolled, Moderate-to-Severe Asthma: The Phase 3 VOYAGE Study. *American Thoracic Society 2021*. 2021;D7 - D007 ADVANCES IN ASTHMA THERAPIES. Available from: https://conference.thoracic.org/program/abstract-search.php?sid=P5839.

3 electronic Medicines Compendium (eMC). *Dupixent 300 mg solution for injection in pre-filled syringe.* Available from: https://www.medicines.org.uk/emc/product/8553#PHARMACOLOGICAL_PROPS [Accessed 2 April 2021]

4 Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: A review of its use in the treatment of atopic dermatitis. *J Am Acad Dermatol*. 2018 Mar;78(3 Suppl 1):S28-S36. Available from: https://doi.org/10.1016/j.jaad.2017.12.022.

5 EU Clinical Trials Register. *A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Children 6 to <12 Years of Age with Uncontrolled Persistent Asthma.* 2021. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-001607-23/results [Accessed 2 April 2021]

6 Barranco P P-AE, Dominguez-Ortega J, Quirce S. Dupilumab in the management of moderate-to-severe asthma: the data so far. *Therapeutics and Clinical Risk Management*. 2018;13:1139-1149. Available from: https://doi.org/10.2147/TCRM.S125964.

7 ClinicalTrials.gov. *Dupilumab - Phase III clinical trial.* Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Dupilumab&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=Sanofi&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 2 April 2021]

8 ClinicalTrials.gov. *Dupilumab - Phase II.* Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Dupilumab&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=Sanofi&lead=&id=&cntry

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=&state=&city=&dist=&locn=&phase=1&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 2 April 2021]
9 National Health Service. *Overview - asthma.* Available from: https://www.nhs.uk/conditions/asthma/ [Accessed 2 April 2021]
10 National Health Service. *Symptoms - asthma.* Available from: https://www.nhs.uk/conditions/asthma/symptoms/ [Accessed 5 April 2021].
11 National Health Service. *Causes - asthma.* Available from: https://www.nhs.uk/conditions/asthma/causes/ [Accessed 5 April 2021].
12 Licari A, Manti S, Castagnoli R, Leonardi S, Marseglia GL. Measuring inflammation in paediatric severe asthma: biomarkers in clinical practice. *Breathe*. 2020;16(1):190301. Available from: https://doi.org/10.1183/20734735.0301-2019.
13 Asthma UK. *Asthma facts and statistics.* 2017. Available from: https://www.asthma.org.uk/about/media/facts-and-statistics/ [Accessed 5 April 2021].
14 NHS England. *Childhood asthma.* Available from: https://www.england.nhs.uk/childhood-asthma/ [Accessed 5 April 2021].
15 Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Medicine*. 2016 2016/08/29;14(1):113. Available from: https://doi.org/10.1186/s12916-016-0657-8.
16 NHS England. *Hospital Admitted Patient Care and Adult Critical Care Activity 2019-20*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20
17 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality: 2019*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset
18 National Health Service. *Treatment - asthma.* Available from: https://www.nhs.uk/conditions/asthma/treatment/ [Accessed 5 April 2021].
19 Scottish Intercollegiate Guidance Network. *British guideline on the management of asthma.* 2019. Available from: https://www.sign.ac.uk/sign-158-british-guideline-on-the-management-of-asthma [Accessed 15 April 2021].
20 Asthma GIF. *Difficult-To-Treat & Severe Asthma in adolescent and adult patients.* 2019. Available from: https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf [Accessed 15 April 2021].
21 UK A. *What is severe asthma?* 2020. Available from: https://www.asthma.org.uk/advice/severe-asthma/what-is-severe-asthma/#latest [Accessed 17 May 2021].
22 Trivedi M, Denton E. Asthma in Children and Adults-What Are the Differences and What Can They Tell us About Asthma? *Frontiers in pediatrics*. 2019;7:256-. Available from: https://doi.org/10.3389/fped.2019.00256.
23 National Institute of Health and Care Excellence (NICE). *Asthma: diagnosis, monitoring and chronic asthma management.* 2017. Available from: https://www.nice.org.uk/guidance/ng80/chapter/Recommendations#pharmacological-treatment-pathway-for-children-and-young-people-aged-5-to-16 [Accessed 15 April 2021].
24 National Insitute for Health and Care Excellence. *Dupilumab for treating severe asthma [ID1213] - Final scope.* 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10276/documents/final-scope [Accessed 15 April 2021].
25 National Insitute for Health and Care Excellence. *Omalizumab for treating severe persistent allergic asthma.* 2013. Available from: https://www.nice.org.uk/guidance/ta278/chapter/1-Guidance [Accessed 15 April 2021].
26 electronic Medicines Compendium. *Nucala 100 mg powder for solution for injection.* 2021. Available from: https://www.medicines.org.uk/emc/product/1938/smpc#INDICATIONS [Accessed 15 April 2021].
27 British National Formulary (BNF). *Dupilumab.* Available from: https://bnf.nice.org.uk/medicinal-forms/dupilumab.html [Accessed 15 April 2021].

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