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Newcastle University

Health Technology Briefing
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Dupilumab for eosinophilic oesophagitis in paediatric patients

Company/Developer	Sanofi

☐ New Active Substance ☒ Significant Licence Extension (SLE)

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Licensing and Market Availability Plans

Currently in phase III clinical trial.

Summary

Dupilumab is in clinical development for the treatment of paediatric patients with active eosinophilic oesophagitis (EoE). EoE is an allergic inflammation of the oesophagus that usually results from a food allergy. Eosinophils are a kind of white blood cell activated by an allergic reaction, which causes eosinophils to build up in the lining of the oesophagus, resulting in swelling of the oesophagus and symptoms such as difficulty in swallowing, abdominal pain, reflux-like symptoms, vomiting/regurgitation, feeding problems and failure to thrive. The lining of the oesophagus may undergo remodelling changes, responsible for the characteristic symptoms and complications of EoE. Research is ongoing and will likely lead to revisions in the treatment of EoE, as there is currently an unmet need for appropriate treatment options.

Dupilumab is a monoclonal antibody (a type of specialised protein) that blocks the action of proteins called interleukins (IL)-4 and IL-13, which both play a major role in causing the signs and symptoms of EoE, characterised by inflammation. It is given as an injection under the skin. If licensed, dupilumab will provide a novel treatment option for paediatric patients with active EoE.

Proposed Indication

Treatment of paediatric patients with active Eosinophilic oesophagitis (EoE).[1]

Technology

Description

Dupilumab (Dupixent, REGN668, SAR231893)[2,3] is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signalling. Dupilumab inhibits 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). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.[4]

Dupilumab is currently in phase III clinical development for the treatment of EoE in paediatric patients. The phase III clinical trial EoE KIDS (NCT04394351) is a randomised control trial, with three experimental parts. Part A was a 16-week double-blind treatment period where participants received high dose/low dose of dupilumab or placebo via subcutaneous (SC) administration, based on body weight. Part B was a 36-week extended active treatment period where participants received a high dose/low dose of dupilumab or placebo via SC administration. Part C was a 108-week open-label extension period where all participants received the higher dose of SC dupilumab with no matching placebo. Tiered dosing regimens based on body weight were used for all participants.[1]

Key Innovation

The most effective available medical therapy for EoE is swallowed topical corticosteroids (fluticasone propionate and budesonide), which have two main drawbacks: they are related to well-known adverse effects (especially in the paediatric population), and there are not enough long-term data to confirm that they are able to reverse the remodelling process of the oesophageal mucosa, which is the major cause of EoE symptoms (including dysphagia, abdominal pain, nausea, obstruction, perforation and vomiting).[5]

Dupilumab targets the type 2 cytokines IL-4 and IL-13. They are involved in the pathogenesis of EoE, therefore, dupilumab has been hypothesised to provide a potential treatment for EoE.[6] In a phase III trial of dupilumab in paediatric patients with active EoE, the trial met its primary endpoint of histological disease remission at 16 weeks with both higher and lower dose weight-tiered regimens.[7] If licensed, dupilumab will provide a novel treatment option for EoE paediatric patients, and the first medicine to alleviate key signs of EoE in children as young as 1 year of age.[8]

Regulatory & Development Status

Dupilumab has a Marketing Authorisation in the UK for the following indications:[4]

- treatment of severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy.
- add-on maintenance treatment for severe asthma in children aged 6 to 11 years of age with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Dupilumab is in phase II/III clinical development for the following conditions in children:[9]

- EoE
- asthma
- chronic spontaneous urticaria and chronic cold urticaria
- prevention of asthma exacerbation

- moderate to severe atopic dermatitis
- cow milk allergy
- multi food allergy
- peanut allergy
- allergic fungal rhinosinusitis
- chronic spontaneous urticaria in patients who remain symptomatic despite the use of antihistamines

Dupilumab has the following awards/designations:

- US FDA Orphan designation for EoE in May 2017.[10]
- US FDA Breakthrough therapy designation for EoE in September 2020.[11]

Patient Group

Disease Area and Clinical Need

EoE is a chronic immune-mediated, inflammatory disorder of the digestive system in which large numbers of a particular type of white blood cell called eosinophils are present in the oesophagus. Eosinophils are part of the immune system and play a role in immune regulation and fighting certain infection, and their accumulation is a hallmark of allergic diseases. The production and accumulation of eosinophils may be caused by many factors such as immune hypersensitivity responses to particular foods or environmental proteins (allergens) in some affected individuals.[12] It is manifested clinically by symptoms of oesophageal dysfunction and histologically by eosinophil-dominant infiltration of the oesophageal mucosa.[13] Young children usually present with nonspecific symptoms such as feeding difficulties, vomiting, abdominal pain, failure to develop normal eating patterns such as not advancing past liquids/soft solids, and occasionally failure to thrive.[14] EoE may occur at any age with a mean age at the time of diagnosis ranging between 5.4 and 9.6 years in children.[6] Eosinophilic Diseases are often found in those with a family history of allergic diseases such as rhinitis, asthma and/or eczema. In fact a personal history of atopy (a predisposition to develop allergic diseases) is found prior to EoE diagnosis in 50-60% of cases.[15]

A large meta-analysis, which included studies from North America, Europe and Australia, estimated incidence and prevalence rates in children of 5.1 cases/100,000 persons/year and 19.1 cases/100,000 persons, respectively.[16] In England (2021-22), there were 20,798 finished consultant episodes (FCE) and 17,830 admissions for oesophagitis (ICD-10 code K20) which resulted in 13,626 FCE bed days and 15,812 day cases.[17]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatment options for paediatric patients with EoE.

Brighton and Sussex University Hospitals NHS Trust recommends oral viscous budesonide solution (OVB) for EoE in paediatric patients.[5]

British Society of Gastroenterology and British Society of Paediatric Gastroenterology Haematology and Nutrition, recommends oral viscous budesonide solution and Proton pump inhibitors particularly omeprazole for treating EoE in children.[18]

Clinical Trial Information

Trial	**EoE KIDS**, NCT04394351, 2019-003078-24 A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab in Paediatric Patients With Active Eosinophilic Esophagitis **Phase III**: Active, not recruiting **Locations**: USA and Canada **Primary completion date:** June 2022
Trial Design	Randomised, parallel assigned, placebo-controlled, quadruple masking
Population	N=102, children aged 1-11 years, body weight of 5-60kg with documented diagnosis of EoE, with confirmed intraepithelial eosinophilic infiltration by endoscopic biopsies.
Intervention(s)	SC administration of dupilumab single-use, prefilled syringe conducted in three parts. A (16-weeks) and B (36-weeks) consisted of two dose types (high and low), based on body weight. Part C (108-weeks) was open-label with all patients receiving higher exposure dupilumab SC administration based on body weight.
Comparator(s)	Matched placebo, part C had no comparator.
Outcome(s)	Proportion of patients achieving peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf (400×) [Time Frame: At Week 16]. See trial record for full list of other outcomes
Results (efficacy)	Preliminary results at 16 weeks, 68% of children on higher dose and 58% of patients on lower dose dupilumab achieved the primary endpoint of significant histological disease remission (peak oesophageal intraepithelial eosinophil count of ≤6 eosinophils [eos]/high power field [hpf]) compared to 3% of children on placebo (p<0.0001 for both). Additionally, at 16 weeks, children receiving higher dose dupilumab experienced the following changes 86% reduction in peak oesophageal intraepithelial eosinophil count from baseline compared to a 21% increase for placebo (p<0.0001). A 0.88 and 0.84 reduction from baseline in disease severity and extent, respectively, as measured at the microscopic level in biopsy specimens compared to a 0.02 and 0.05 increase for placebo (both p<0.0001). A 3.5-point reduction in abnormal endoscopic findings from baseline compared to a 0.3-point increase for placebo (p<0.0001).[8]
Results (safety)	For the 16-week treatment period, overall rates of adverse events (AEs) were 79% for dupilumab and 91% for placebo. Adverse events more commonly (≥5%) observed with dupilumab compared to placebo included COVID-19 (21% dupilumab, 0% placebo) (all cases were mild or moderate), a rash (9% dupilumab, 6% placebo), viral gastroenteritis (6% dupilumab, 3% placebo), diarrhoea (6% dupilumab, 3% placebo), nausea (6% dupilumab, 0% placebo). Headache (8% dupilumab, 3% placebo).[8]

Estimated Cost

Dupilumab is already marketed in the UK for various indications; two 150mg/1ml pre-filled pen/syringes or two 175mg/1ml pre-filled pen/syringes cost £1,264.89.[3]

Relevant Guidance

NICE Guidance

No relevant guidance identified

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Specialised allergy services. E03/S/j.

Other Guidance

- British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Haematology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults 2022.[18]
- United European Gastroenterology. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults 2017.[19]

Additional Information

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