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Newcastle University

Health Technology Briefing
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Dupilumab for treating Chronic Spontaneous Urticaria in people aged 12 years and older after 1 previous treatment

Company/Developer	Sanofi

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27643	NICE ID: 10423	UKPS ID: 657281

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Dupilumab is in clinical development for the treatment of chronic spontaneous urticaria for people who still have symptoms despite previous treatment. Urticaria is a skin disorder where red, raised, itchy rashes appear on the skin. Urticaria is considered chronic once symptoms have been present for six weeks or longer and appear almost daily. Spontaneous urticaria occurs when there is no clear trigger that brings on urticaria symptoms. People who do not respond to treatment with antihistamines or a biological therapy known as omalizumab currently have limited further treatment options.

Dupilumab is a human monoclonal antibody, which is a manufactured version of an immune protein created by the body to fight infection. It is given as an injection under the skin. Dupilumab stops the action of two immune response mediators, interleukin-4 (IL-4) and interleukin-13 (IL-13). These proteins are responsible for inflammation in the body and blocking them decreases levels of inflammation. Levels of IL-4 and IL-13 are raised in people with chronic urticaria, which means that blocking these proteins is a promising treatment option for patients who have been unsuccessful with treatment despite multiple treatment options.

Proposed Indication

Treatment of adolescents and adults aged 12 years and older with chronic spontaneous urticaria (CSU) who are refractory to H1 antihistamine treatment.[1]

Technology

Description

Dupilumab (Dupixent) is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling. It 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 decreases many of the mediators of type 2 inflammation in patients.[2]

Dupilumab is currently in phase III clinical development for the treatment of adolescents and adults aged 12 years and older with CSU who remain symptomatic despite H1 antihistamine treatment. In a phase III clinical trial (CUPID, NCT04180488), participants received dupilumab via subcutaneous (SC) injection at an unspecified dose and schedule. Participants also received unspecified non-sedating H1 antihistamine treatment.[1]

Key Innovation

CSU treatment can include antihistamines, oral corticosteroids and omalizumab, however some patients are still not able to achieve a good treatment response with these options.[3] IL-4 and/or IL-13 serum levels of CSU patients have been shown to be elevated and the inhibition of IL-4 and IL-3 signalling (such as with dupilumab) may potentially be beneficial to patients with urticaria.[4]

Small case studies have demonstrated positive activity of dupilumab in CSU treatment and further positive clinical activity in the form of significantly improved itch and urticaria relief has been reported in the results of a portion of the pivotal CUPID trial.[3,5]

Regulatory & Development Status

Dupilumab has a Marketing Authorisation in the UK for the following indications:[2]

- Treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy
- Treatment of severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy
- Add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma 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

Dupilumab as a monotherapy and in addition to various other medicinal products is being developed for the following indications in phase II and III clinical trials:[6]

- Peanut allergy
- Atopic dermatitis
- Grass allergy
- Allergic broncopulmonary aspergillosis

- Asthma
- Eosinophilic esophagitis
- Atopic hand and foot dermatitis
- Bullous pemphigoid
- Chronic rhinosinusitis with nasal polyps
- Allergic fungal rhinosinusitis
- Chronic obstructive pulmonary disease (COPD)
- Cold urticaria
- Prurigo nodularis
- Keloids
- Chronic hepatic pruritus
- Prostate cancer
- Contact dermatitis
- Hand eczema
- Cholinergic urticaria
- Atopic keratoconjunctivitis
- Cow's milk allergy
- Aspirin-exacerbated respiratory disease
- Eosinophilic gastritis

Patient Group

Disease Area and Clinical Need

Urticaria is a disorder of the skin characterised by red, raised, itchy rashes appearing superficially on the skin. CSU is a form of urticaria that is chronic (lasting 6 weeks or longer) and has no clearly identifiable cause of disease. Mast cells are believed to the major effector cell in the pathology of urticaria. The degranulation of mast cells and subsequent release of histamine is the main reason for the development of rash-like symptoms.[7]

Chronic urticaria has been reported to have a lifetime prevalence of 2-3%.[8] It can therefore be estimated based on 2020 population estimates, that 1,022,537-1,533,806 people in England and Wales will experience chronic urticaria during at least one point in their life.[9] In England in 2020-21 there were 5,917 hospital admissions and 6,318 finished consultant episodes (FCE) for urticaria (ICD-10 L50).[10]

Recommended Treatment Options

Currently recommended options for the treatment of chronic urticaria include:[8,11]

- Avoidance of triggers (if triggers are identifiable)
- Non-sedating H1 antihistamine treatment
- Oral corticosteroid treatment for severe symptoms
- Omalizumab treatment following inadequate response to antihistamines
- Leukotriene receptor antagonist treatment following inadequate response to antihistamines
- Cyclosporine treatment following inadequate response to antihistamines
- Mycophenolate mofetil treatment following inadequate response to antihistamines
- Topical antipruritic treatment following inadequate response to antihistamines

Clinical Trial Information

Trial	**CUPID**, NCT04180488, EudraCT2019-003775-19; Master Protocol of Two Randomized, Double-blind, Placebo Controlled, Multi-center, Parallel-group Studies of Dupilumab in Patients With Chronic Spontaneous Urticaria (CSU) Who Remain Symptomatic Despite the Use of H1 Antihistamine Treatment in Patients naïve to Omalizumab and in Patients Who Are Intolerant or Incomplete Responders to Omalizumab **Phase III:** active, not recruiting **Locations:** EU, UK, USA, Canada and other countries **Primary completion date:** April 2022
Trial Design	Randomised, parallel assignment, quadruple masking, placebo controlled
Population	N=234; children, adolescents and adults aged 6 to 80 years; diagnosis of CSU refractory to H1 antihistamines; diagnosis of CSU less than 6 months ago; presence of itch and hives for greater than 6 consecutive weeks; omalizumab naïve; intolerant or incomplete responder to omalizumab
Intervention(s)	Dupilumab (SC injection) and non-sedating H1-antihistamine (oral administration)
Comparator(s)	Placebo (SC injection) and non-sedating H1-antihistamine (oral administration)
Outcome(s)	Primary outcomes: • Change from baseline in weekly itch severity score (except EU and EU reference countries) [Time frame: baseline to week 24]: Change from baseline in weekly itch severity score (ISS7) at week 24 • For EU and EU reference countries only: change from baseline in weekly urticaria activity score [Time frame: baseline to week 24]: Change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at week 24 See trial record for full list of other outcomes.
Results (efficacy)	• 63% reduction in itch severity with Dupilumab vs 35% with standard-of-care (antihistamines) as measured by a 0-21-point itch severity scale (10.24-point reduction with Dupixent vs 6.01-point reduction with standard-of-care) ($p<0.001$), the primary endpoint in the US (secondary endpoint in the EU) with continuous improvement out to week 24. • 65% reduction in urticaria activity (itch and hives) severity with Dupilumab vs 37% with standard-of-care, as measured by a 0-42-point urticaria activity scale, (20.53-point reduction with Dupixent vs 12.00-point reduction with standard-of-care) ($p<0.001$), the primary endpoint in the EU (secondary endpoint in the US) with continuous improvement out to week 24.[5]
Results (safety)	For the 24-week treatment period, the occurrence of treatment emergent adverse events were generally similar between the Dupixent and placebo groups (50% of Dupixent patients and 59% of placebo patients). The most common adverse events were injection site reactions (11% Dupixent, 13% placebo).[5]

Clinical Trial Information

Trial	**DUPICSU, NCT03749135;** A Multicenter, Randomized, Double-blind, Placebo-controlled, Proof-of-concept Phase 2, 16-week Treatment Study With a 16 Week Follow-up Period to Assess the Efficacy and Safety of Dupilumab (Anti-IL4Ra) in Adult Patients With Chronic Spontaneous Urticaria Despite H1-antihistamine Treatment. **Phase II**: unknown **Location:** Germany **Primary completion date:** April 2022
Trial Design	Randomised, parallel assignment, quadruple masking, placebo controlled
Population	N=72; adults aged 18 to 75 years with ongoing CSU; moderate to severe; refractory to standard of care treatment; UAS7 score equal or more than 16
Intervention(s)	Dupilumab (SC injection)
Comparator(s)	Placebo (SC injection)
Outcome(s)	Urticaria activity score over 7 days (UAS7) [Time frame: change from 7 days prior to baseline to 7 days prior to week 16]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Dupilumab is already marketed in the UK for various indications; a 300mg/2ml pre-filled pen/syringe and a 200mg/1.14ml pre-filled pen/syringe cost £1,264.89.[12]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Ligelizumab for previously treated chronic spontaneous urticarial in people 12 years and over. Expected date of issue to be confirmed.
- NICE technology appraisal. Omalizumab for previously treated chronic spontaneous urticaria (TA339). June 2015.
- NICE evidence summary. Chronic urticarial: off-label doses of cetirizine (ESUOM31). July 2014.
- NICE Clinical Knowledge Summary. Urticaria. 2021.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract For Specialised Allergy Services (All Ages). B09/S/b.
- NHS England. 2013/14 NHS Standard Contract For Specialised Dermatology Services (All Ages). A12/S/a.

Other Guidance

- Powell RJ, Leech SC, Till S, Huber PA, Nasser SM et al. BSACI guideline for the management of chronic urticarial and angioedema. 2015.[8]
- Grattan CEH, Humphreys F, British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for evaluation and management of urticaria in adults and children. 2007.[13]

Additional Information

References

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6 Clinicaltrials.gov. *Dupilumab - Phase II and III clinical trials.* 2021. 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+OR+Regeneron&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 26 October 2021].

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