

## HEALTH TECHNOLOGY BRIEFING JUNE 2019

### Dupilumab for children aged 6 to less than 12 years with severe atopic dermatitis

|                   |        |         |        |
|-------------------|--------|---------|--------|
| NIHRIO ID         | 20632  | NICE ID | 9848   |
| Developer/Company | Sanofi | UKPS ID | 650241 |

|   |                                       |
|---|---------------------------------------|
| Licensing and market availability plans | Currently in phase III clinical trial |
|---|---------------------------------------|

### SUMMARY

Dupilumab is in development for the treatment of children aged  $\geq 6$  to  $< 12$  years with severe atopic dermatitis (AD) uncontrolled with currently available therapies. AD is a chronic inflammatory skin disease that affects both children and adults and is characterised by redness, itchiness, and scaling of the skin. Some people only have small patches of dry skin, but others may experience widespread red, inflamed skin all over the body. Patients with moderate to severe AD could come across with sleep disturbances, anxiety, depression, and poor quality of life. Currently, the management of AD involves the removal or treatment of trigger factors that contribute to the development of the disease.

Dupilumab acts by blocking certain proteins called interleukin-4 (IL-4) and interleukin-13 (IL-13) and mediating the pathways involved in the inflammatory process in AD. Dupilumab is taken subcutaneously (SC) and is currently licensed for the treatment of moderate to severe AD in adults who are candidates for systemic therapy. If licensed, dupilumab will offer an additional treatment option for children aged  $\geq 6$  to  $< 12$  years with severe AD.

## PROPOSED INDICATION

Children aged  $\geq 6$  to  $< 12$  years with severe atopic dermatitis (AD) uncontrolled with currently available therapies.<sup>a, 1</sup>

## TECHNOLOGY

### DESCRIPTION

Dupilumab (Dupixent) is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling. Dupilumab inhibits IL-4 signalling via the type I receptor (IL-4R $\alpha$ / $\gamma$ c), and both IL-4 and IL-13 signalling through the type II receptor (IL-4R $\alpha$ /IL-13R $\alpha$ ).<sup>2</sup> IL-4 and IL-13 are cytokines central to the pathogenesis of 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<sup>+</sup> Th2-cell population in secondary lymphoid organs.<sup>3</sup> Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.<sup>2</sup>

Dupilumab is currently in phase III clinical development for the treatment of severe AD. In phase III clinical trial NCT03345914, participants aged  $\geq 6$  to  $< 12$  years with severe AD were randomised to three arms. Participants receive dupilumab 150 mg/mL subcutaneously (SC), 175 mg/mL and matching placebo in groups 1, 2 and 3 respectively. In all three groups, all participants are required to initiate treatment with a medium potency topical corticosteroids using a standardised regimen. It is recommended that participants use triamcinolone acetonide 0.1% cream, fluocinolone acetonide 0.025% cream, or clobetasone butyrate 0.05%. Furthermore, all subjects are required to apply moisturisers throughout the study. All types of moisturisers are permitted, but subjects may not initiate treatment with prescription moisturisers. Subjects may continue using stable doses of such moisturisers if initiated before the screening visit.<sup>1,4</sup>

### INNOVATION AND/OR ADVANTAGES

Dupilumab has been licenced for use in the EU and UK for the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy.<sup>2</sup> Dupilumab is being assessed for the treatment of severe AD in a new target population (children aged  $\geq 6$  to  $< 12$  years).<sup>a, 1,4</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, dupilumab is licensed in the EU/UK for the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy.<sup>2</sup>

The most common adverse reaction were injection site reactions, conjunctivitis, blepharitis, and oral herpes.<sup>2</sup>

Besides severe AD treatment, dupilumab is currently in phase III clinical development for the treatment of the following conditions:<sup>5</sup>

- Asthma
- Chronic obstructive pulmonary disease

<sup>a</sup> Information provided by Sanofi on the UK PharmaScan

- Nasal polyps
- Eosinophilic oesophagitis

Dupilumab is in phase II clinical development for the treatment of the following conditions:<sup>6</sup>

- Nasal polyps
- Asthma
- Allergic rhinitis
- Eosinophilic oesophagitis
- Cholinergic urticarial
- Peanut allergy
- Chronic spontaneous urticaria

## PATIENT GROUP

### DISEASE BACKGROUND

AD also known as eczema or atopic eczema, is a chronic inflammatory skin disease characterised by erythema, pruritus, and scaling of skin that affects both children and adults.<sup>7,8</sup> AD has a complex and heterogeneous aetiology, characterised histologically by skin infiltration of inflammatory cells, predominantly lymphocytes, eosinophils, and mast cells.<sup>9</sup>

Although the pathogenesis and aetiology of AD remain to be completely understood, this multifactorial disease likely results from complex crosstalk between genetic and environmental factors.<sup>10,11</sup> It can run in families and often develops alongside other conditions, such as asthma and hay fever. The symptoms of AD often have certain triggers, such as soaps, detergents, stress and the weather. Sometimes allergies can be started by food.<sup>12</sup> Exaggerated Th2-type response, disruption of the epidermal barrier functions, high level of serum IgE, and decreased production of antimicrobial peptides (AMPs) are the key findings in AD.<sup>10,11</sup>

Some people only have small patches of dry skin, but others may experience widespread red, inflamed skin all over the body. Although AD can affect any part of the body, it most often affects the hands, insides of the elbows, backs of the knees and the face and scalp in children.<sup>12</sup>

For patients with moderate to severe AD, skin lesions encompassing large surface areas are often associated with severe itching. These lesions can cause sleep disturbances and, in turn, symptoms of anxiety, depression, and poor quality of life.<sup>13</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

Estimates of the prevalence of AD vary.<sup>14</sup> AD affects both sexes equally and usually starts in the first months of life. In the UK, 15-20% (affecting 1 in 5 children in the UK) of school-aged children have AD.<sup>14,15</sup> Evidence from several UK based studies shows that in children aged 1-5 years in the UK, 84% were considered to have mild AD, 14% moderate, and 2% severe (n = 1760, dermatologist's rating). In older children in the UK (aged 5-10 years), similar figures were reported: mild AD in 80% of children, moderate in 18% and severe in 2% (n = 137). The International Study of Asthma and Allergies in Childhood (ISAAC) study reported that the 12 month period prevalence of severe eczema in the UK was 2.0%.<sup>16</sup>

According to Hospital Episode Statistics (HES) data for 2017-18 there were:<sup>17</sup>

- 13 primary diagnosis for other atopic dermatitis (ICD-10: L20.8) in the age group 5 -14 years old of which:
  - 10 were 5-9 years old

- 3 were 10-14 years old
- 241 primary diagnosis for atopic dermatitis, unspecified (ICD-10: L20.9) in the age group 5 -14 years old of which:
  - 126 were 5-9 years old
  - 115 were 10-14 years old

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

Dermatitis has several causes, which may influence treatment. Management of dermatitis involves the removal or treatment of contributory factors that may trigger the development of the disease or worsen a flare. The management of AD also involve the use of different therapies to ease the symptoms.<sup>18,19</sup>

For the treatment of AD, NICE recommend a stepped approach . Treatment can be stepped up or down according to the severity of the condition and includes a range of therapies such as emollients, bandages, phototherapy and topical and oral corticosteroids.<sup>20</sup>

### CURRENT TREATMENT OPTIONS

The following treatment options have been recommended for severe AD:<sup>18,21,22</sup>

- Emollients
- Potent topical corticosteroids - these include betamethasone valerate 0.1% and betamethasone dipropionate 0.05%, provided in creams, ointments, lotion, or gel
- Topical tacrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged 2 years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy
- Bandages - general practitioner (GP) may prescribe special medicated bandages, clothing or wet wraps to wear over areas of skin affected by eczema. These can be used over emollients or with topical corticosteroids to prevent scratching
- Phototherapy
- Oral antihistamines
- Oral antibiotics

### PLACE OF TECHNOLOGY

If licensed, dupilumab will offer an additional treatment option for patients aged 6 to less than 12 years old with severe AD uncontrolled with currently available therapies.

## CLINICAL TRIAL INFORMATION

|                              |  |
|------------------------------|--|
| <b>Trial</b>                 | <a href="#">NCT03345914</a> , R668-AD-1652, <a href="#">EudraCT 2016-004997-16</a> ; aged ≥ 6 to < 12 years; phase III |
| <b>Sponsor</b>               | Regeneron Pharmaceuticals  |
| <b>Status</b>                | Ongoing  |
| <b>Source of Information</b> | Trial registry <sup>1,4</sup>  |
| <b>Location</b>              | EU countries (incl UK), USA and Canada   |

|                           |  |
|---------------------------|--|
| <b>Design</b>             | Randomised, placebo-controlled, double-blind study   |
| <b>Participants</b>       | N=367 (enrolled); aged $\geq 6$ to $< 12$ years; children diagnosed with AD according to the American Academy of Dermatology consensus criteria (Eichenfield 2003) at screening visit; chronic AD diagnosed at least 1 year prior to the screening visit; Investigator's Global Assessment (IGA) = 4 at screening and baseline visits; Eczema Area and Severity Index (EASI) $\geq 21$ at the screening and baseline visits; Body Surface Area (BSA) $\geq 15\%$ at screening and baseline visits; documented recent history (within 6 months before the baseline visit) of inadequate response to topical AD medication(s); and at least 11 (of a total of 14) applications of a stable dose of topical emollient (moisturiser) twice daily during the 7 consecutive days immediately before the baseline visit.  |
| <b>Schedule</b>           | <p>Participants were randomised to one of the treatment arms:</p> <ol style="list-style-type: none"> <li>1. Dupilumab, dosing regimen 1, subcutaneous (SC)</li> <li>2. Dupilumab, dosing regimen 2, SC</li> <li>3. Matching placebo solution for injection SC</li> </ol> <p>All participants are required to initiate treatment with a medium potency topical corticosteroids using a standardized regimen. It is recommended that participants use triamcinolone acetonide 0.1% cream, fluocinolone acetonide 0.025% cream, or clobetasone butyrate 0.05%. All types of moisturizers are permitted, but subjects may not initiate treatment with prescription moisturizers. Subjects may continue using stable doses of such moisturizers if initiated before the screening visit.</p>  |
| <b>Follow-up</b>          | Participants will be followed up from baseline to week 16.   |
| <b>Primary Outcomes</b>   | <ul style="list-style-type: none"> <li>• Proportion of participants with Investigator's Global Assessment (IGA) "0" or "1" (on a 5-point scale) at week 16</li> </ul>  |
| <b>Secondary Outcomes</b> | <p>Time frame: 16 weeks</p> <ul style="list-style-type: none"> <li>• Proportion of patients with Eczema Area and Severity Index (EASI)-75 (<math>\geq 75\%</math> improvement from baseline)</li> <li>• Percent change in EASI score from baseline to week 16</li> <li>• Percent change from baseline to week 16 in weekly average of daily worst itch score</li> <li>• Change from baseline to week 16 in weekly average of daily worst itch score</li> <li>• Proportion of participants with EASI-50 (<math>\geq 50\%</math> improvement from baseline)</li> <li>• Proportion of participants with EASI-90 (<math>\geq 90\%</math> improvement from baseline)</li> <li>• Change from baseline to week 16 in percent Body Surface Area (BSA) affected by AD</li> <li>• Percent change from baseline to week 16 in Scoring Atopic Dermatitis (SCORAD)</li> <li>• Proportion of participants with improvement (reduction) of weekly average of daily worst itch score <math>\geq 4</math> from baseline</li> <li>• Proportion of participants with improvement (reduction) of weekly average of daily worst itch score <math>\geq 3</math> from baseline</li> <li>• Time to onset of effect on pruritus during the 16-week treatment period (<math>\geq 4</math> point reduction of weekly average of daily worst itch score from baseline)</li> <li>• Time to onset of effect on pruritus during the 16-week treatment period (<math>\geq 3</math> point reduction of weekly average of daily worst itch score from baseline)</li> </ul> |

|                                |   |
|--------------------------------|---|
|                                | <ul style="list-style-type: none"> <li>• Change from baseline to week 16 in Children's Dermatology Life Quality Index (CDLQI)</li> <li>• Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM)</li> <li>• Change from baseline to week 16 in Dermatitis Family Index (DFI)</li> <li>• Change from baseline to week 16 in Patient Reported Outcomes Measurements Information Systems (PROMIS) pediatric anxiety short form scale score</li> <li>• Change from baseline to week 16 in PROMIS pediatric depressive symptoms short form scale score</li> <li>• Topical treatment for AD - proportion of TCS medication-free days from baseline to week 16</li> <li>• Mean weekly dose of TCS in grams for low and medium potency TCS from baseline to week 16</li> <li>• Mean weekly dose of TCS in grams for high potency TCS from baseline to week 16</li> <li>• Incidence of skin-infection Treatment-emergent adverse events (TEAEs) (excluding herpetic infections) through week 16</li> <li>• Incidence of serious TEAEs through week 16</li> </ul> |
| <b>Key Results</b>             | -   |
| <b>Adverse effects (AEs)</b>   | -   |
| <b>Expected reporting date</b> | Estimated primary completion date in Jun 2019   |

## ESTIMATED COST

Dupilumab is already marketed in the UK for the treatment of moderate to severe AD; two pre-filled disposable injections (150 mg/1 ml) cost £1,264.89.<sup>23</sup>

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal guidance. Tacrolimus and pimecrolimus for atopic eczema (TA82). August 2004.
- NICE technology appraisal guidance. Frequency of application of topical corticosteroids for atopic eczema (TA81). August 2004.
- NICE clinical guideline. Atopic eczema in under 12s: diagnosis and management (CG57). December 2007.
- NICE quality standard. Atopic eczema in under 12s (QS44). September 2013.

### 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

- Ring et al. Guidelines for treatment of atopic eczema (atopicdermatitis) Part I. 2012.<sup>24</sup>
- Ring et al. Guidelines for treatment of atopic eczema (atopicdermatitis) Part II. 2012.<sup>25</sup>
- Scottish Intercollegiate Guidelines Network (SIGN). Management of atopic eczema in primary care: A national clinical guideline (SIGN 125). March 2011.<sup>26</sup>

## ADDITIONAL INFORMATION

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