

**NIHR Innovation Observatory
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**Dupilumab for children aged 12 years to 17 years
with moderate to severe atopic dermatitis**

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LAY SUMMARY

Atopic dermatitis (AD) or atopic eczema is a very common skin condition due to skin inflammation. It is usually a long-term condition where the skin becomes itchy, dry, cracked, sore and red. About one in every five children in the UK have AD. This condition may have impacts on the affected child's quality of life. AD cannot be cured although it can improve significantly, or even clear completely, in some children as they get older. There is an unmet need for safe and effective long-term treatment for moderate-to-severe AD particularly in children.

Dupilumab is a monoclonal antibody medicine that is currently in development as an injection under the skin (subcutaneous) for the treatment of moderate to severe AD in children. Dupilumab is already licensed in the UK for the treatment of moderate-to-severe atopic dermatitis in adults. If licensed, dupilumab will offer an additional treatment option for children aged 12 years to 17 years with moderate to severe atopic dermatitis uncontrolled on current therapies.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. 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.

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TARGET GROUP

Atopic dermatitis (children aged 12 years to 17 years, moderate to severe uncontrolled on current therapies).

TECHNOLOGY

DESCRIPTION

Dupilumab (Dupixent®; REGN668; SAR231893) is a monoclonal antibody designed for the treatment of atopic diseases such as eczema. It binds to the alpha subunit of the interleukin-4 receptor (IL-4R α). Through blockade of IL-4R α , dupilumab modulates signalling of both the interleukin 4 and interleukin 13 pathway.¹ IL-4 and IL-13 are key type 2 (including Th2) cytokines involved in atopic dermatitis.²

In the phase II clinical trial (NCT02407756; EudraCT: 2014-003263-37), dupilumab was given as a subcutaneous injection at a dose of 150 mg/ml. No further details about the treatment regimen (duration and frequency) have been reported.^{3,4}

Dupilumab is licensed in the UK for the treatment of moderate-to-severe atopic eczema in adults.⁵ Common ($\geq 1\%$ to $< 10\%$) and very common ($>10\%$) adverse reactions associated with dupilumab are conjunctivitis, oral herpes, eosinophilia, headache, conjunctivitis allergic, eye pruritus, blepharitis, injection site reactions.²

Dupilumab is in phase II and phase III stage of development for other indications such as asthma, nasal polyps, and eosinophilic oesophagitis.⁶

INNOVATION and/or ADVANTAGES

There is an unmet need for safe and efficacious long term therapy for the management of moderate-to-severe atopic dermatitis (AD). In clinical trials, dupilumab has demonstrated efficacy by reducing clinical activity and symptoms, and showed improvement in the AD genomic phenotype, including a significant reduction in type 2 T helper (Th2) chemokines and reversal of key epidermal markers of AD. It also has a favorable safety profile.⁷ If licensed, dupilumab will offer an additional treatment option for children aged 12 years to 17 years with moderate to severe atopic dermatitis uncontrolled on current therapies.

DEVELOPER

Sanofi

PATIENT GROUP

BACKGROUND

Atopic dermatitis (AD) or atopic eczema is a very common skin condition due to skin inflammation. AD may start at any age but the onset is often in childhood. It's usually a long-term (chronic) condition, although it can improve significantly, or even clear completely, in some children as they get older.^{8,9}

AD causes the skin to become itchy, dry, cracked, sore and red. Some people only have small patches of dry skin, but others may experience widespread red, inflamed skin all over the body.⁹ AD can affect

any part of the skin, including the face, but the areas that are most commonly affected are the creases in the joints at the elbows and knees, as well as the wrists and neck (called a flexural pattern). Other common appearances of AD include coin-sized areas of inflammation on the limbs (a discoid pattern), and numerous small bumps that coincide with the hair follicles (a follicular pattern).⁸ People with AD usually have periods when symptoms are less noticeable, as well as periods when symptoms become more severe (flare-ups).⁹

The exact cause of AD is unknown. It often occurs in people who get allergies. The word “Atopic” means sensitivity to allergens. It can run in families, and often develops alongside other conditions, such as asthma and hay fever. Soaps, detergents, stress and the weather are triggers to AD symptoms. Sometimes food allergies can play a part, especially in young children with severe eczema.⁹

AD cannot be cured, but there are many ways of controlling it. Most children with AD will see their AD improve as they get older, with 60% clear by their teens. However, many of these people continue to have dry skin and so need to continue to avoid irritants such as soaps, detergents and bubble baths.⁸

It has been reported that the quality of life of children with AD is often impaired, particularly in respect to clothing, holidays, staying with friends, owning pets, swimming or the ability to play or do sports. The impairment of quality of life caused by childhood AD has been shown to be greater than or equal to other common childhood diseases such as asthma and diabetes, emphasising the importance of eczema as a major chronic childhood disease. Restriction of normal family life, difficulties with complicated treatment regimens and increased work in caring for a child with AD lead to parental exhaustion and feelings of hopelessness, guilt, anger and depression. The hidden costs involved in AD management can be significant and have particular impact on lower income families.¹⁰

CLINICAL NEED and BURDEN OF DISEASE

It is estimated that 1 in every 5 children in the UK is affected by AD at some stage⁸ which equates to 771,122 children aged 12-17 years in England and Wales based on the 2016 mid-year population estimate.¹¹

The population likely to be eligible to receive dupilumab could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Dupilumab for treating moderate to severe atopic dermatitis after topical treatments (ID1048). Expected August 2018.
- NICE technology appraisal. Alitretinoin for the treatment of severe chronic hand eczema (TA177). August 2009.
- NICE technology appraisal. Frequency of application of topical corticosteroid for atopic eczema (TA81). August 2004.
- NICE technology appraisal. Tacrolimus and pimecrolimus for atopic eczema (TA82). August 2004
- NICE interventional procedure guidance. Grenz rays therapy for inflammatory skin conditions (IPG236). November 2007.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Dermatology Services (All Ages). A12/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Allergy Services (All Ages). B09/S/b.
- NHS England. 2013/14 NHS Standard Contract for Paediatric Medicine: Specialised Allergy Services. E03/S/j.

OTHER GUIDANCE

- European Dermatology Forum. EDF-Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) Part I. January 2018.¹²
- Scottish Intercollegiate Guidelines Network (SIGN). Management of atopic eczema in primary care. Edinburgh (SIGN publication no. 125). 2011.¹³

CURRENT TREATMENT OPTIONS

There's currently no cure for AD and severe AD often has a significant impact on daily life, which may be difficult to cope with physically and mentally. There's also an increased risk of skin infections. The aim of treatment for AD is to relieve symptoms and include:⁹

- Self-care techniques, such as reducing scratching and avoiding triggers,
- Using emollients (moisturising treatments),
- Topical corticosteroids to reduce swelling, redness and itching during flare-ups.⁹

Topical tacrolimus is recommended by NICE, within its licensed indications, as an option for the second-line treatment of moderate to severe AD 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.¹⁴

Pimecrolimus is recommended by NICE, within its licensed indications, as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged 2 to 16 years 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.¹⁴

It is recommended that treatment with tacrolimus or pimecrolimus be initiated only by physicians (including general practitioners) with a special interest and experience in dermatology, and only after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options.¹⁴

EFFICACY and SAFETY

Trial	NCT03054428 ; children aged ≥ 12 to < 18 years; dupilumab vs placebo; phase III
Sponsor	Regeneron Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry; ¹⁵ Press release ¹⁶
Location	USA and Canada
Design	Randomised, placebo-controlled, double-blind.
Participants	n=251; aged 12-17 years; males and females; diagnosed with AD; Investigator Global Assessment (IGA) ≥ 3 ; Eczema Area and Severity (EASI) ≥ 16 ; Baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity ≥ 4 ; $\geq 10\%$ body surface area (BSA) of AD involvement; recent history of inadequate response to topical AD medication(s) or for whom topical treatments is medically inadvisable.
Schedule	Randomised to dupilumab (dose regimen 1); dupilumab (dose regimen 2); or placebo (dose regimen 3)
Follow-up	Active treatment period: not reported. Follow-up 16 weeks.
Primary Outcomes	Time Frame: at week 16 <ul style="list-style-type: none"> - Proportion of patients with IGA 0 to 1 (on a 5-point scale) - Proportion of patients with EASI-75 ($\geq 75\%$ improvement from baseline)
Secondary Outcomes	Time Frame: at week 16 <ul style="list-style-type: none"> - Proportion of patients with EASI-75 ($\geq 75\%$ improvement from baseline) - Percent change in EASI score - Percent change in weekly average of daily peak Pruritus Numerical Rating Scale (NRS) - Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4 - Change in weekly average of daily peak Pruritus NRS - Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 3 - Proportion of patients with EASI-50 - Proportion of patients with EASI-90 - Change in BSA affected by AD - Percent change in SCORing Atopic Dermatitis (SCORAD) - Change in Children's Dermatology Life Quality Index (CDLQI) - Change in Patient Oriented Eczema Measure (POEM) - Change in Hospital Anxiety and Depression Scale (HADS) - Incidence of skin-infection treatment-emergent adverse events (TEAEs) - Incidence of serious TEAEs Time Frame: at week 4 <ul style="list-style-type: none"> - Percent change in weekly average of daily peak Pruritus (NRS)

	<ul style="list-style-type: none"> - Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥ 4
Key Results	<ul style="list-style-type: none"> • 24% of patients who received weight-based dosing of dupilumab every two weeks (200 mg or 300 mg) and 18% of patients who received a fixed dose of dupilumab every four weeks (300 mg) achieved the primary endpoint – clear or almost-clear skin (IGA; score of 0 or 1) – compared with 2% with placebo (p less than 0.0001, and p=0.0007, respectively). • 41.5% of patients who received dupilumab every two weeks and 38% of patients who received dupilumab every four weeks achieved 75% or greater skin improvement (EASI-75) compared to 8% with placebo (p less than 0.0001). • There was a 66% improvement in the dupilumab every two weeks group and, 65% improvement in the dupilumab every four weeks group in average percent change from baseline in EASI score compared with a 24% improvement in the placebo group (p less than 0.0001). • There was a 48% improvement in the dupilumab every two weeks group and 45.5% improvement in the dupilumab every four weeks group in average percent change from baseline in the pruritus numerical rating scale (NRS) compared with a 19% improvement in the placebo group (p less than 0.0001).
Adverse effects (AEs)	<p>For the 16-week treatment period, the overall rate of adverse events was comparable between the dupilumab groups and placebo (72% for dupilumab every two weeks, 64% for dupilumab every four weeks and 69% for placebo). There were no serious adverse events or events leading to treatment discontinuation in either dupilumab treatment group.</p> <ul style="list-style-type: none"> • Adverse events that were observed at a higher rate with dupilumab included injection site reactions (8.5% for dupilumab every two weeks, 6% for dupilumab every four weeks compared with 3.5% for placebo) and conjunctivitis (10% for dupilumab every two weeks, 11% for dupilumab every four weeks compared with 5% for placebo). • Skin infections were numerically lower in the dupilumab groups (11% for dupilumab every two weeks, 13% for dupilumab every four weeks compared with 20% for placebo).
Expected reporting date	Study completion date reported as July 2018.

Trial	NCT02612454 , EudraCT-2015-001396-40, R668-AD-1434; children aged ≥ 6 months to <18 years; dupilumab; phase III extension.
Sponsor	Regeneron Pharmaceuticals
Status	Enrolling by invitation
Source of Information	Trial registry ^{17,18}
Location	EU (incl UK), USA, and Canada.
Design	Single group assignment, open-label.
Participants	n=765 (planned); aged 6 Months to 17 Years; males and females; participated in a prior dupilumab study in paediatric patients with AD and adequately completed the visits and assessments required for both the treatment and follow-up periods, as defined in the prior study protocol.

Schedule	Participants will receive 150mg/ml or 175mg/ml dupilumab by subcutaneous injection
Follow-up	Active treatment duration: not reported. Follow-up: 272 weeks.
Primary Outcomes	Time Frame: baseline up to week 272 <ul style="list-style-type: none"> - Rate of TEAEs per participant year from baseline through the last study visit - Number of participants with at least one TEAE per participant year from baseline through the last study visit
Secondary Outcomes	Time Frame: baseline up to week 272 <ul style="list-style-type: none"> - Number of treatment-emergent serious adverse events (SAEs) from baseline through the last study visit - Incidence of TEAEs of special interest from baseline through the last study visit - Proportion of participants with an IGA score of 0 or 1 (clear or almost clear) at all in-clinic visits post-baseline - Proportion of participants with EASI-75 ($\geq 75\%$ reduction in EASI from baseline of parent study) response at all in-clinic visits post-baseline - Change from baseline in EASI score at all in-clinic visits post-baseline - Percent change from baseline in EASI at all in-clinic visits post-baseline - Change from BSA affected by AD (BSA) at all in-clinic visits post-baseline - Percent change from baseline SCORAD at all in-clinic visits post-baseline - Change from baseline in CDLQI for participants ≥ 4 years of age at all in-clinic visits post-baseline in which the assessments are planned to be performed - Number of AD flares during the study - Annualise event rate of AD flares during the study - Proportion of participants with at least one flare during the study - Proportion of well-controlled weeks Time Frame: baseline up to week 260 <ul style="list-style-type: none"> - Proportion of responders (defined as participants with IGA 0 or 1) who maintain IGA 0 or 1 during at least 75% of the subsequent visits during the treatment period - For responders (defined as participants with IGA 0 or 1), median percentage of subsequent visits during the treatment period, at which IGA 0 or 1 is maintained
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as October 2023.

Trial	NCT02407756 , EudraCT-2014-003263-37, R668-AD-1412; children aged ≥ 6 to < 18 years; dupilumab dosing regimen 1 vs dupilumab dosing regimen 2; phase IIa
Sponsor	Regeneron Pharmaceuticals
Status	Completed

Source of Information	Trial registry; ¹⁹ Presentation. ²⁰
Location	EU (incl UK) and Canada
Design	Non-randomised, single group assignment, open-label
Participants	n=78; aged 6-17 years; males and females; AD; disease cannot be adequately controlled with topical medications; IGA = 3 or 4
Schedule	Participants aged 12-17 years were allocated to 2 mg/kg dupilumab vs 4 mg/kg dupilumab.
Follow-up	Active treatment duration: not specified. Follow-up: 20 weeks
Primary Outcomes	Characterisation of the PK profile of dupilumab in pediatric patients with AD [Time frame: baseline to week 12]
Secondary Outcomes	Time frame: baseline to week 12 <ul style="list-style-type: none"> - Incidence of AEs - Percent change from baseline in EASI score - Percent change from baseline in peak pruritus NRS score - Percent change from baseline in SCORAD score - Percentage of patients with an IGA score of 0 or 1
Key Results	Dupilumab administered both as single dose or as multiple weekly doses appeared safe and demonstrated preliminary efficacy in this open-label study. Overall the PK profile of dupilumab in these pediatric patients with AD is generally consistent with that observed in adults with moderate-to-severe AD; exposure was comparable between the two age groups studied at the same dose levels. The 2 mg/kg and 4 mg/kg dose regimens showed similar improvements in efficacy endpoints.
Adverse effects (AEs)	Adverse effects reported were skin infection (adjudicated), nasopharyngitis, dermatitis atopic, and injection-site reactions. While the 4 mg/kg dose was associated with more AEs, it did not lead to an increase in permanent discontinuations
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Dupilumab is already marketed in the UK for the treatment of moderate-to-severe atopic eczema in adults (specialist use only). The NHS indicative price for Dupixent 300mg/2ml solution for injection pre-filled syringes (Sanofi) (2 pre-filled disposable injection) is £1264.89.⁵

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: It is well known that the parents or carers of children with atopic dermatitis are negatively impacted by the disease. For example carers report broken sleep and consequent tiredness. This may lead to impact on quality of life, employment (or education) and depression and anxiety. Similarly relationships are put under strain and there are financial implications for the family. In recognition of this there has been recent research to develop tools to quantify the impact on atopic dermatitis on patients parents. (see for example Dermatology 232(4) · August 2016).^a
- Evidence is not currently available from the trial program but the company expect that these impacts on the parents and carers of patients who respond to dupilumab treatment will be reduced.^a
- No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs
- Reduced drug treatment costs

^a Information provided by the company

Other increase in costs

Other reduction in costs: The parents and carers of patients often seek out additional remedies over and above those prescribed. These may include expensive creams and lotions not available on prescription, specialist clothing and foods. It is likely therefore that in addition to decreased drug and other direct costs to the NHS there will be a reduction in out of pocket expenditure for families of patients with atopic dermatitis who respond to dupilumab. Patients may require courses of phototherapy. These can involve multiple sessions over several weeks or months. A reduction in the need for this intervention may lead to lower travel costs and reductions in the requirement for time off work for parents and carers.^b

Evidence is not currently available from the paediatric trial program to suggest that the use of existing systemic treatments such as immunosuppressants and oral steroids will be significantly reduced. (This is available to a certain extent from the adult studies). However for patients who respond to dupilumab lower exposure to these treatments might be expected and in the longer term, reductions in may lead to decreases in side effects requiring additional treatment. For example continued use of oral steroids can lead to endocrine issues and steroid induced osteoporosis. Longer term use of immunosuppressants can lead to kidney complications (ciclosporin) and gastric issues (methotrexate).^b

Other

None identified

OTHER ISSUES

Clinical uncertainty or other research question identified

None identified

^b Information provided by the company

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