Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING MARCH 2019

Baricitinib for moderate to severe atopic dermatitis

NIHRIO ID	17241	**NICE ID**	9885
Developer/Company	Eli Lilly and Company Ltd	**UKPS ID**	650049

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

SUMMARY

Baricitinib is in development for the treatment of adults with moderate to severe atopic dermatitis (AD) which is also known as eczema or atopic eczema. AD is a chronic inflammatory skin disease that affects both children and adults and is characterized 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.

Baricitinib acts by selectively and reversibly blocking the janus-associated kinase (JAK) enzymes that mediate the pathways involved in the inflammatory process in AD and other inflammatory diseases. Baricitinib is taken orally and is currently licensed for the treatment of moderate to severe active rheumatoid arthritis in adult patients that have not responded well to other therapies. If licensed, baricitinib will offer an additional treatment option for adults with moderate to severe AD.

PROPOSED INDICATION

Adults with moderate to severe atopic dermatitis (AD) who are candidates for systemic therapy.[a 1-3]

TECHNOLOGY

DESCRIPTION

Baricitinib (Olumiant, LY3009104) is a selective and reversible inhibitor of the janus-associated kinase (JAK) activity. JAKs are enzymes that mediate the transduction of intracellular signals involved in the process of inflammatory diseases. Baricitinib selectively inhibits the activity of JAK1 and JAK2 to a greater degree than the JAK3 and tyrosine kinase 2 subtypes.[4,5]

Baricitinib is currently in phase III clinical development for the treatment of adults with moderate to severe atopic dermatitis (AD) who have had inadequate response or intolerance to existing topical medications. In phase III clinical trials (BREEZE-AD1; NCT03334396, BREEZE-AD2; NCT03334422, BREEZE-AD3; NCT03334435; BREEZE-AD4; NCT03428100, BREEZE-AD5; NCT03435081, BREEZE-AD6; NCT03559270, BREEZE-AD7; NCT03733301), participants were randomised to receive high (4 mg), mid (2 mg), and low (1 mg) doses of baricitinib orally or placebo for 16 weeks.[1-3,6-14]

INNOVATION AND/OR ADVANTAGES

The Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway are activated by the stimulation of several cellular receptors by numerous growth factors and cytokines.[15] JAK-STAT pathway is involved in signal transduction of numerous dermatologically relevant cytokines such as interferon (IFN)-γ, IFN-α, interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21, IL-5, IL-6, IL-12, IL-13 and IL-23.[16]

Various inflammatory skin diseases are caused by mediators which activate a JAK-STAT pathway. Selective JAK-inhibitors influence the phosphorylation and activation of different JAKs which results in the blockage of the cascade of inflammatory cytokines.[17]

Baricitinib is a novel oral therapy which specifically targets the JAK-STAT inflammatory pathways involved in AD.[18]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, baricitinib is licensed in the EU/UK for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (as monotherapy or in combination with methotrexate).[4]

The most commonly reported adverse events (≥ 10%) among patients receiving baricitinib monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (DMARDs) are increased low-density lipoprotein (LDL) cholesterol (33.6%) and upper respiratory tract infections (14.7%).[4]

Baricitinib is currently in phase III clinical development for the treatment of the following conditions:[19]

- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Paediatric atopic dermatitis

[a] Information provided by pharmaceutical company on the UK PharmaScan

- Axial spondyloarthritis
- Psoriatic arthritis

Baricitinib is currently in phase II clinical development for the treatment of the following conditions:[20]

- Crohn's disease
- Alcohol-induced liver decompensation

PATIENT GROUP

DISEASE BACKGROUND

Atopic dermatitis (AD) also known as eczema or atopic eczema, is a chronic inflammatory skin disease characterized by erythema, pruritus, and scaling of skin that affects both children and adults.[21,22] AD has a complex and heterogeneous aetiology, characterized histologically by skin infiltration of inflammatory cells, predominantly lymphocytes, eosinophils, and mast cells.[23]

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.[24,25] 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.[26] Exaggerated helper T-cells (Th2-type) response, disruption of the epidermis barrier functions, high level of serum IgE, and decreased production of antimicrobial peptides (AMPs) are the key findings in AD.[24,25]

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.[26]

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.[27]

CLINICAL NEED AND BURDEN OF DISEASE

Although AD presents most frequently in childhood, it can present at any age.[28,29] Estimates vary due to the different population examined, but figures suggest that it affects about 10-30% of children and 2-10% of adults.[22,29-36] There is no difference in prevalence based on sex and ethnicity.[37,38]

It is indicated that AD affects 1 in 12 adults in the UK.[39] A 2016 international, cross-sectional, web-based survey estimated the prevalence of atopic dermatitis in several countries including the UK. Size of the sample population in the UK was 10,001. The prevalence of atopic dermatitis in this UK cohort was 2.5% [95% Confidence Interval (CI): 2.2%, 2.8%]. The prevalence was the same among males and females (2.5%). 32% of the cases were severe, and 56% were moderate cases.[40]

According to the 2017-18 Hospital Episodes Statistics data, collectively there were 1,130 admissions which resulted in 632 day cases and 1,622 FCE bed days for other atopic dermatitis and atopic dermatitis unspecified (ICD-10 codes: L20.8 and L20.9 respectively) in England.[41]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Dermatitis has several causes, which may influence treatment. Management of dermatitis involves the removal or treatment of contributory factors to the development of the disease or worsen a flare. Beyond of removing the disease trigger factors, the management of AD also involve the use of different therapies to ease the symptoms.[42,43]

For the treatment of AD, the NICE recommend a stepped approach according to severity disease. 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.[44]

CURRENT TREATMENT OPTIONS

The following treatment options have been recommended for moderate AD:[31-33,43,45,46]

- Emollients
- Moderate potency topical corticosteroids - these include betamethasone valerate 0.025% and clobetasone butyrate 0.05%, provided in creams, ointments, lotion, or gel
- Topical calcineurin inhibitor (tacrolimus or pimecrolimus) –for eczema in sensitive sites not responding to simpler treatment
- 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
- Dupilumab – recommended for adults with moderate to severe AD who have not responded to at least 1 other systemic therapy or these are contraindicated or intolerant

Following treatment options have been recommended for severe AD:[43-47]

- Emollients
- Potent topical corticosteroids - these include betamethasone valerate 0.1% and betamethasone dipropionate 0.05%, provided in creams, ointments, lotion, or gel
- Topical calcineurin inhibitor (tacrolimus or pimecrolimus) – are recommended for eczema in sensitive sites not responding to simpler treatment
- 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 corticosteroids
- Dupilumab - recommended for adults with moderate to severe AD who have not responded to at least 1 other systemic therapy or these are contraindicated or intolerant
- Alitretinoin – indicated for the treatment of severe chronic hand eczema refractory to potent topical corticosteroids

PLACE OF TECHNOLOGY

If licensed, baricitinib will offer an additional treatment option for adults with moderate to severe atopic dermatitis who are candidates for systemic therapy.

CLINICAL TRIAL INFORMATION

Trial	BREEZE-AD1, NCT03334396, 16580, EudraCT 2017-000870-12; baricitinib *vs.* placebo; phase III
Sponsor	Eli Lilly and Company
Status	Completed
Source of Information	Trial registry[2,6,48]
Location	EU countries (not including the UK) and other countries
Design	Randomised, placebo-controlled, double-blind study
Participants	N=600 (estimated); aged 18 years and older; moderate to severe AD for at least 12 months; have had inadequate response or intolerance to existing topical medications within 6 months
Schedule	Participants are randomised to one of the treatment arms:[6] 1. Baricitinib high dose (4 mg) versus placebo, both administered orally; 2. Baricitinib mid dose (2 mg) versus placebo, both administered orally; 3. Baricitinib low dose (1 mg) versus placebo, both administered orally; 4. Placebo administered orally.
Follow-up	Participants will be followed for 16 weeks (time point of assessment of endpoint). After 16 weeks, partients can enter the long-term extension study, BREEZE-AD3
Primary Outcomes	Proportion of participants achieving Investigator's Global Assessment (IGA) of 0 or 1 with a ≥ 2 Point Improvement [Time frame: 16 weeks]
Secondary Outcomes	Time frame at 16 weeks: • Proportion of participants achieving Eczema Area and Severity Index 75 (EASI75) • Proportion of participants achieving EASI90 • % change from baseline in EASI Score • Proportion of participants achieving SCORing Atopic Dermatitis 75 (SCORAD75) • Proportion of participants achieving a 4-point improvement in itch Numeric Rating Scale (NRS) • Change from baseline in the score of Item 2 of the Atopic Dermatitis Sleep Scale (ADSS) • Change from baseline in the skin pain NRS • Proportion of participants achieving EASI50 • Proportion of participants achieving IGA of 0 • Change from baseline in SCORAD • Proportion of participants achieving SCORAD90 • Change from baseline in Body Surface Area (BSA) affected • Proportion of participants developing skin infections requiring antibiotic treatment • % change from baseline in itch NRS • Change from baseline in the total score of the Patient Oriented Eczema Measure (POEM) • Change from baseline in the Patient Global Impression of Severity—Atopic Dermatitis (PGI-S-AD) score • Change from baseline on the Hospital Anxiety Depression Scale (HADS) • Change from baseline in the Dermatology Life Quality Index (DLQI) • Change from baseline on the Work Productivity and Activity Impairment - Atopic Dermatitis (WPAI-AD) questionnaire

	• Change from baseline on the European Quality of Life-5 Dimensions 5 Levels (EQ-5D-5L)
Key Results	Baricitinib met the primary endpoint in BREEZE-AD1. The investigational trial, compared to patients treated with placebo, a statistically significant proportion of patients treated with baricitinib achieved the primary endpoint at week 16 defined by the Investigator's Global Assessment for AD (IGA) score of clear or almost clear (IGA 0,1). Company plans to share the full data results from BREEZE-AD1 study at future scientific venues and in peer-reviewed journals.[48]
Adverse effects (AEs)	In the 16-week placebo-controlled phase of BREEZE-AD1, the incidence of treatment-emergent adverse events and serious adverse events with baricitinib treatment was similar to placebo, and the most common treatment-emergent adverse events observed were nasopharyngitis and headache. No venous thromboembolic events (VTEs), major adverse cardiovascular events (MACE), or deaths were reported.[48]
Expected reporting date	Estimated primary completion date July 2019. Estimated study completion date August 2019.

Trial	BREEZE-AD2, NCT03334422, 16581, EudraCT 2017-000871-10; baricitinib *vs.* placebo; phase III
Sponsor	Eli Lilly and Company
Status	Completed
Source of Information	Trial registry[3,7,48]
Location	EU countries (not including the UK) and other countries
Design	Randomised, placebo-controlled, double-blind study
Participants	N=750 (enrolled); aged 18 years and older; moderate to severe AD for at least 12 months; have had inadequate response or intolerance to existing topical medications within 6 months
Schedule	Participants are randomised to one of the treatment arms:[7] 1. Baricitinib high dose (4 mg) versus placebo, both administered orally; 2. Baricitinib mid dose (2 mg) versus placebo, both administered orally; 3. Baricitinib low dose (1 mg) versus placebo, both administered orally; 4. Placebo administered orally.
Follow-up	Participants will be followed for 16 weeks (time point of assessment of the endpoint). After 16 weeks, partients can enter the long-term extension study, BREEZE-AD3
Primary Outcomes	Proportion of participants achieving Investigator's Global Assessment (IGA) of 0 or 1 with a ≥ 2 Point Improvement [Time frame: 16 weeks]
Secondary Outcomes	Time frame at 16 weeks • Proportion of participants achieving Eczema Area and Severity Index 75 (EASI75) • Proportion of participants achieving EASI90 • % change from baseline in EASI Score • Proportion of participants achieving SCORing Atopic Dermatitis 75 (SCORAD75) • Proportion of participants achieving a 4-point improvement in itch Numeric Rating Scale (NRS) • Change from baseline in the score of Item 2 of the Atopic Dermatitis Sleep Scale (ADSS) • Change from baseline in the skin pain NRS

	• Proportion of participants achieving EASI50 • Proportion of participants achieving IGA of 0 • Change from baseline in SCORAD • Proportion of participants achieving SCORAD90 • Change from baseline in Body Surface Area (BSA) affected • Proportion of participants developing skin infections requiring antibiotic treatment • % change from baseline in itch NRS • Change from baseline in the total score of the Patient Oriented Eczema Measure (POEM) • Change from baseline in the Patient Global Impression of Severity—Atopic Dermatitis (PGI-S-AD) score • Change from baseline on the Hospital Anxiety Depression Scale (HADS) • Change from baseline in the Dermatology Life Quality Index (DLQI) • Change from baseline on the Work Productivity and Activity Impairment - Atopic Dermatitis (WPAI-AD) questionnaire • Change from baseline on the European Quality of Life-5 Dimensions 5 Levels (EQ-5D-5L)
Key Results	Baricitinib met the primary endpoint in BREEZE-AD2. The investigational trial, compared to patients treated with placebo, a statistically significant proportion of patients treated with baricitinib achieved the primary endpoint at Week 16 defined by the Investigator's Global Assessment for AD (IGA) score of clear or almost clear (IGA 0,1). Lilly plans to share the full data results from BREEZE-AD2 study at future scientific venues and in peer-reviewed journals.[48]
Adverse effects (AEs)	In the 16-week placebo-controlled phase of BREEZE-AD2, the incidence of treatment-emergent adverse events and serious adverse events with baricitinib treatment was similar to placebo, and the most common treatment-emergent adverse events observed were nasopharyngitis and headache. No venous thromboembolic events (VTEs), major adverse cardiovascular events (MACE), or deaths were reported.[48]
Expected reporting date	Estimated primary completion date December 2018. Estimated study completion date December 2018.

Trial	BREEZE-AD3, NCT03334435, 16587, EudraCT 2017-000873-35; baricitinib *vs.* placebo; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	Trial registry[1,8]
Location	EU countries (not including the UK) and other countries
Design	Randomised, placebo-controlled, double-blind study
Participants	N=1,500 (estimated); aged 18 years and older; moderate to severe AD for at least 12 months; have had inadequate response or intolerance to existing topical medications within 6 months. Must have completed ≥16 weeks of study treatment in originating study – BREEZE-AD1, 2 or 7.
Schedule	Participants are randomised to one of the treatment arms:[8] 1. Baricitinib high dose (4 mg) versus placebo, both administered orally; 2. Baricitinib mid dose (2 mg) versus placebo, both administered orally; 3. Baricitinib low dose (1 mg) versus placebo, both administered orally; 4. Placebo administered orally.

Follow-up	Participants will be followed for 52 weeks (time point of assessment of the endpoint).
Primary Outcomes	• Proportion of participants with a response of Investigator's Global Assessment (IGA) of 0 or 1 [Time frame: 16 weeks] • Proportion of participants achieving IGA 0 or 1 [Time frame: 36 weeks] • Proportion of participants achieving IGA 0 or 1 [Time frame: 52 weeks]
Secondary Outcomes	• Proportion of participants achieving IGA 0, 1 or 2 [Time frame: 52 weeks] • Proportion of participants achieving IGA 0 or 1 (non-responders) [Time frame: 52 weeks] • Proportion of participants achieving response of Eczema Area and Severity Index (EASI) 75 from baseline of originating study [Time frame: 52 weeks] • Proportion of participants with a 4-point improvement from baseline of originating study in itch NRS [Time frame: 16 weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date July 2021. Estimated study completion date August 2021.

Trial	BREEZE-AD4, NCT03428100, 16841, EudraCT 2017-004574-34; baricitinib in combination with topical corticosteroids *vs.* placebo; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	Trial registry[9,14]
Location	EU countries (including the UK) and other countries
Design	Randomised, placebo-controlled, double-blind study
Participants	N=500 (estimated); aged 18 years and older; moderate to severe AD for at least 12 months; have had inadequate response or intolerance to existing topical medications within 6 months
Schedule	Participants are randomised to one of the treatment arms:[14] 1. Baricitinib high dose (4 mg) in combination with topical corticosteroids versus placebo, both administered orally; 2. Baricitinib mid dose (2 mg) in combination with topical corticosteroids versus placebo, both administered orally; 3. Baricitinib low dose (1 mg) in combination with topical corticosteroids versus placebo, both administered orally; 4. Placebo in combination with topical corticosteroids administered orally.
Follow-up	Participants will be followed for 16 weeks (time point of assessment of the endpoint).
Primary Outcomes	• Proportion of participants achieving Investigator's Global Assessment (IGA) of 0 or 1 with a ≥ 2 point improvement (high or mid dose) [Time frame: 16 weeks]
Secondary Outcomes	• Proportion of participants achieving IGA of 0 or 1 with a ≥ 2 point improvement (low dose) [Time frame: 16 weeks] • Proportion of participants achieving Eczema Area and Severity Index (EASI) 75 [Time frame: 16 weeks] • Proportion of participants achieving EASI90 [Time frame: 16 weeks] • Percent Change from Baseline in EASI Score [Time frame: 16 weeks]

	• Proportion of Participants Achieving SCORing Atopic Dermatitis (SCORAD75) [Time Frame: 16 Weeks] • Proportion of Participants Achieving a 4-Point Improvement in Itch Numeric Rating Scale (NRS) [Time Frame: 16 Weeks] • Change from Baseline in the Score of Item 2 of the Atopic Dermatitis Sleep Scale (ADSS) [Time Frame: Baseline, 16 Weeks] • Change from Baseline in Skin Pain NRS [Time Frame: Baseline, 16 Weeks] • Proportion of Participants Achieving EASI50 [Time Frame: 16 Weeks] • Proportion of Participants Achieving IGA of 0 [Time Frame: 16 Weeks] • Change from Baseline in SCORAD [Time Frame: Baseline, 16 Weeks] • Proportion of Participants Achieving SCORAD90 [Time Frame: 16 Weeks] • Change from Baseline in Body Surface Area (BSA) Affected [Time Frame: Baseline, 16 Weeks] • Proportion of Participants Developing Skin Infections Requiring Antibiotic Treatment [Time Frame: 16 Weeks] • Mean Number of Days without Topical Corticosteroids (TCS) Use [Time Frame: 16 Weeks] • Mean Gram Quantity of TCS Use (Tube Weights) [Time Frame: 16 Weeks] • Percent Change from Baseline in Itch NRS [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the Total Score of the Patient Oriented Eczema Measure (POEM) [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the Patient Global Assessment of Severity -Atopic Dermatitis (PGI-S-AD) Score [Time Frame: Baseline, 16 Weeks] • Change from Baseline on the Hospital Anxiety Depression Scale (HADS) [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the Dermatology Life Quality Index (DLQI) [Time Frame: Baseline, 16 Weeks] • Change from Baseline on the Work Productivity and Activity Impairment - Atopic Dermatitis (WPAI-AD) Questionnaire [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Score [Time Frame: Baseline, 16 Weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date June 2019. Estimated study completion date March 2021.

Trial	BREEZE-AD5, NCT03435081, 17049; baricitinib *vs.* placebo; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	Trial registry[10]
Location	Canada, Puerto Rico and United States
Design	Randomised, placebo-controlled, double-blind study
Participants	N=450 (estimated); aged 18 years and older; moderate to severe AD, including EASI score ≥ 16, IGA score of ≥ 3 and ≥ 10% of BSA involvement; have had inadequate response or intolerance to existing topical medications within 6 months
Schedule	Participants are randomised to one of the treatment arms:

	1. Baricitinib high dose versus placebo, both administered orally; 2. Baricitinib low dose versus placebo, both administered orally; 3. Placebo administered orally.
Follow-up	Participants will be followed for 16 weeks (time point of assessment of the endpoint).
Primary Outcomes	Proportion of participants achieving Investigator's Global Assessment (IGA) of 0 or 1 with a ≥ 2 point improvement [Time frame: 16 weeks]
Secondary Outcomes	• Proportion of participants achieving Eczema Area and Severity Index (EASI) 75 [Time frame: 16 weeks] • Proportion of participants achieving EASI90 [Time frame: 16 weeks] • Percent Change from Baseline in EASI Score [Time frame: 16 weeks] • Proportion of Participants Achieving SCORing Atopic Dermatitis (SCORAD75) [Time Frame: 16 Weeks] • Proportion of Participants Achieving a 4-Point Improvement in Itch Numeric Rating Scale (NRS) [Time Frame: 16 Weeks] • Change from Baseline in the Score of Item 2 of the Atopic Dermatitis Sleep Scale (ADSS) [Time Frame: Baseline, 16 Weeks] • Change from Baseline in Skin Pain NRS [Time Frame: Baseline, 16 Weeks] • Proportion of Participants Achieving EASI50 [Time Frame: 16 Weeks] • Proportion of Participants Achieving IGA of 0 [Time Frame: 16 Weeks] • Change from Baseline in SCORAD [Time Frame: Baseline, 16 Weeks] • Proportion of Participants Achieving SCORAD90 [Time Frame: 16 Weeks] • Change from Baseline in Body Surface Area (BSA) Affected [Time Frame: Baseline, 16 Weeks] • Proportion of Participants Developing Skin Infections Requiring Antibiotic Treatment [Time Frame: 16 Weeks] • Percent Change from Baseline in Itch NRS [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the Total Score of the Patient Oriented Eczema Measure (POEM) [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the Patient Global Assessment of Severity -Atopic Dermatitis (PGI-S-AD) Score [Time Frame: Baseline, 16 Weeks] • Change from Baseline on the Hospital Anxiety Depression Scale (HADS) [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the Dermatology Life Quality Index (DLQI) [Time Frame: Baseline, 16 Weeks] • Change from Baseline on the Work Productivity and Activity Impairment - Atopic Dermatitis (WPAI-AD) Questionnaire [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Score [Time Frame: Baseline, 16 Weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date August 2019. Estimated study completion date May 2021.

Trial	BREEZE-AD6, NCT03559270, 17064; baricitinib; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	Trial registry[11]

Location	Canada, Puerto Rico and United States
Design	Open-label
Participants	N=300 (estimated); aged 18 years and older; have had discontinued from study JAIW, and completed at least 16 weeks on treatment
Schedule	Participants received baricitinib administered orally
Follow-up	Participants will be followed for 116 weeks, includes a treatment period of approximately 104-weeks and up to 11 planned study visits
Primary Outcomes	Proportion of participants achieving Investigator's Global Assessment (IGA) of 0 or 1 [Time frame: 16 weeks]
Secondary Outcomes	• Proportion of participants achieving Eczema Area and Severity Index (EASI) 75 [Time frame: 16 weeks] • Proportion of Participants Achieving a Body Surface Area of ≤3% [Time Frame: Week 16] • Proportion of Participants Achieving a ≥4-Point Improvement in Itch Numeric Rating Scale (NRS) [Time Frame: Week 16]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date December 2019. Estimated study completion date September 2021.

Trial	BREEZE-AD7, NCT03733301, 17100, EudraCT 2018-001726-26; baricitinib in combination with topical corticosteroids *vs.* placebo; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	Trial registry[12,13]
Location	EU countries (not including the UK) and other countries
Design	Randomised, placebo-controlled, double-blind study
Participants	N=300 (estimated); aged 18 years and older; moderate to severe AD for at least 12 months; have had inadequate response or intolerance to existing topical medications within 6 months
Schedule	Participants are randomised to one of the treatment arms: 1. Baricitinib high dose (4 mg) in combination with topical corticosteroids versus placebo, both administered orally; 2. Baricitinib low dose (2 mg) in combination with topical corticosteroids versus placebo, both administered orally; 3. Placebo in combination with topical corticosteroids administered orally.
Follow-up	Participants will be followed for 16 weeks (time point of assessment of the endpoint).
Primary Outcomes	Proportion of participants achieving Investigator's Global Assessment (IGA) of 0 or 1 with a ≥ 2 point improvement [Time frame: 16 weeks]
Secondary Outcomes	• Proportion of participants achieving Eczema Area and Severity Index (EASI) 75 [Time frame: 16 weeks] • Proportion of participants achieving EASI90 [Time frame: 16 weeks] • Percent Change from Baseline in EASI Score [Time frame: 16 weeks] • Proportion of Participants Achieving SCORing Atopic Dermatitis (SCORAD75) [Time Frame: 16 Weeks]

	• Proportion of Participants Achieving a 4-Point Improvement in Itch Numeric Rating Scale (NRS) [Time Frame: 16 Weeks] • Change from Baseline in the Score of Item 2 of the Atopic Dermatitis Sleep Scale (ADSS) [Time Frame: Baseline, 16 Weeks] • Change from Baseline in Skin Pain NRS [Time Frame: Baseline, 16 Weeks] • Proportion of Participants Achieving EASI50 [Time Frame: 16 Weeks] • Proportion of Participants Achieving IGA of 0 [Time Frame: 16 Weeks] • Change from Baseline in SCORAD [Time Frame: Baseline, 16 Weeks] • Proportion of Participants Achieving SCORAD90 [Time Frame: 16 Weeks] • Change from Baseline in Body Surface Area (BSA) Affected [Time Frame: Baseline, 16 Weeks] • Proportion of Participants Developing Skin Infections Requiring Antibiotic Treatment [Time Frame: 16 Weeks] • Mean Gram Quantity of Topical Corticosteroids (TCS) Use (Tube Weights) [Time Frame: 16 Weeks] • Percent Change from Baseline in Itch NRS [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the Total Score of the Patient Oriented Eczema Measure (POEM) [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the Patient Global Assessment of Severity -Atopic Dermatitis (PGI-S-AD) Score [Time Frame: Baseline, 16 Weeks] • Change from Baseline on the Hospital Anxiety Depression Scale (HADS) [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the Dermatology Life Quality Index (DLQI) [Time Frame: Baseline, 16 Weeks] • Change from Baseline on the Work Productivity and Activity Impairment - Atopic Dermatitis (WPAI-AD) Questionnaire [Time Frame: Baseline, 16 Weeks] • Change from Baseline in the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Score [Time Frame: Baseline, 16 Weeks] • Mean Number of Days without Use of Background TCS [Time Frame: Baseline through 16 Weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date July 2019. Estimated study completion date August 2021.

ESTIMATED COST

Baricitinib is already marketed in the UK for the treatment of moderate-to-severe active rheumatoid arthritis in patients who have had an inadequate response to, or are intolerant to, one or more disease-modifying anti-rheumatic drugs (as monotherapy or in combination with methotrexate; a 2 mg costs £805.56/a pack of 28 tablets. A 4 mg costs £805.56/a pack of 28 tablets and cost £2,416.68/a pack of 84 tablets.[49]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology Appraisal Guidance. Dupilumab for treating moderate to severe atopic dermatitis (TA534). August 2018.
- NICE Technology Appraisal Guidance. Alitretinoin for the treatment of severe chronic hand eczema (TA177). August 2009.
- 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.

NHS ENGLAND (POLICY/COMMISSIONING) 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

- Wollenberg A; Barbarot S; Bieber T; et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. January 2018.[50]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of atopic eczema in primary care: a national clinical guideline (SIGN 125). March 2011.[51]
- American Academy of Dermatology (AAD). Atopic dermatitis clinical guideline (2014).[52]

REFERENCES

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