

## HEALTH TECHNOLOGY BRIEFING OCTOBER 2021

### Lebrikizumab for moderate to severe atopic dermatitis

NIHRIO ID	10872	NICE ID	10396
Developer/Company	Almirall Ltd	UKPS ID	658273

Licensing and market availability plans	Currently in phase III clinical trials.
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### SUMMARY

Lebrikizumab is being developed for patients (aged 12 years to adult) with moderate to severe atopic dermatitis (AD). 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 experience 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.

Lebrikizumab is a novel drug designed to bind to a protein called IL-13 and inhibit its biological effects. IL-13 is believed to drive multiple aspects of the pathophysiology underlying the range of signs and symptoms of AD by promoting type 2 inflammation and mediating its effects on tissue, resulting in skin barrier dysfunction, itch, skin thickening and infection. If licensed, lebrikizumab will offer an additional treatment option for patients with moderate to severe AD.

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

## PROPOSED INDICATION

For the treatment of patients (12 years and older) with moderate to severe atopic dermatitis (AD) with a history of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable.<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Lebrikizumab (TNX-650) is a monoclonal antibody designed to bind interleukin 13 (IL-13) with very high affinity, specifically preventing the formation of the IL-13R $\alpha$ 1/IL-4R $\alpha$  heterodimer complex and subsequent signalling, thereby inhibiting the biological effects of IL-13 in a targeted fashion. IL-13 is believed to be a central pathogenic mediator that drives multiple aspects of the pathophysiology of AD.<sup>2,3</sup>

In the phase III clinical trial (NCT04146363), lebrikizumab was given as subcutaneous (SC) injection in a number of different ways. One arm of the trial treated participants in an induction period with lebrikizumab every 2 weeks as a loading dose at baseline and week 2, followed by a single injection every 2 weeks from week 4 until week 14. Participants were then treated in a maintenance period with lebrikizumab once every 2 weeks from week 16 to week 52. Another arm of the trial treated participants in a maintenance period only with lebrikizumab once every 4 weeks from week 16 to week 52. The final arm of the trial treated participants who required rescue treatment in a maintenance period with lebrikizumab once every 2 weeks from week 16 to week 52.<sup>1</sup>

### INNOVATION AND/OR ADVANTAGES

AD is a heterogeneous disease with signs and symptoms varying greatly between patients, underscoring the need for additional treatment options with different mechanisms of action.<sup>4</sup> Efficacy of topical therapies can be limited, and their frequent use is cumbersome and carries the risk for side effects. Standard systemic treatments used for moderate-to-severe disease also carry significant risks.<sup>5</sup>

IL-13 cytokines and inflammatory pathways have been identified as important for the pathophysiology of AD. Lebrikizumab binds specifically to IL-13 and it has been theorised that targeting the most central pathologic mediators of AD, such as IL-13, can maximize efficacy and limit toxicity for patients.<sup>5,6</sup> Evidence supports the hypothesis that selective antagonism of IL-13 is sufficient to control AD, providing an improvement in the patient's quality of life. If approved, lebrikizumab would be an additional therapy that specifically targets IL-13, part of a new phase in the management of AD.<sup>7</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lebrikizumab is not currently licensed for any other indications in the EU/UK.

In August 2021, the U.S. Food and Drug Administration (FDA) granted Fast Track designation to lebrikizumab for moderate-to-severe AD in adult and adolescent patients (aged 12 to less than 18 years of age and weighing at least 40 kg).<sup>4</sup>

Lebrikizumab is also in phase III clinical trials for asthma and phase II trials for chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.<sup>8</sup>

## 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. AD has a complex and heterogeneous aetiology, characterised histologically by skin infiltration of inflammatory cells, predominantly lymphocytes, eosinophils, and mast cells.<sup>9</sup> AD affects both males and females equally.<sup>10</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>11,12</sup> The symptoms of AD can have certain triggers, such as soaps, detergents, stress and the weather.<sup>13</sup> An exaggerated response from type 2 helper T-cells (Th2); disruption of the epidermal barrier functions; high level of serum Immunoglobulin E; decreased production of antimicrobial peptides (AMPs) are the key characteristics in AD. 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>11,12</sup>

The appearance and location of AD changes with age. In infants it mainly affects the face and limb extensor surfaces. In adolescents and adults, it is most commonly localised and found on the flexural surfaces of the body, anterior and lateral neck, eyelids, forehead, scalp, face, wrists, dorsa of the feet, and hands.<sup>14</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>15</sup> 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.<sup>16</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

Estimates of the prevalence of AD vary however it has been suggested that the UK has a high prevalence of AD, affecting 11-20% of children and 5-10% of adults.<sup>17</sup> If these figures are applied to the 2020 England and Wales mid-year population estimate, there are an estimated 2,804,162 – 5,535,718 people over the age of 12 with AD.<sup>18</sup>

The majority of people with AD experience mild disease (80%) and around 2-4% experience severe disease.<sup>19</sup> According to the 2020-21 Hospital Episodes Statistics data, for primary diagnosis, collectively there were 1,018 finished consultant episodes (FCE), 549 admissions which resulted in 583 day cases and 1,235 FCE bed days for 'other AD' and 'AD unspecified' (ICD-10 codes: L20.8 and L20.9) in England.<sup>20</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

Treatment of AD focuses on the alleviation of symptoms and limiting exposure to contributory factors that may trigger the development of the disease or worsen a flare. In addition, patients can use different therapies to ease symptoms.<sup>21</sup> There is no cure, but many children find their symptoms naturally improve as they get older.<sup>22</sup>

For the treatment of AD, NICE recommends 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, topical and oral corticosteroids, topical calcineurin inhibitors, phototherapy, systemic immunosuppressant therapies, biological systemic treatment and finally best supportive care.<sup>21</sup>

### CURRENT TREATMENT OPTIONS

People with moderate or severe dermatitis not responding to topical treatments may be referred to secondary care and treated with stronger oral medications such as oral steroids or systemic immunosuppressants (azathioprine, ciclosporin, mycophenolate mofetil and methotrexate).<sup>23</sup>

NICE recommends the following biological systemic treatments for moderate to severe AD if the disease has not responded to at least 1 systemic immunosuppressant, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are not suitable:<sup>24</sup>

- Baricitinib
- Dupilumab

### PLACE OF TECHNOLOGY

If licensed, lebrikizumab will offer an additional treatment option for patients (12 years and older) with moderate to severe atopic dermatitis (AD) with a history of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	<b>ADvocate1</b> , <a href="#">NCT04146363</a> , <a href="#">2019-002932-10</a> ; A Randomized, Double-blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab in Patients With Moderate to Severe Atopic Dermatitis <b>Phase III</b> - Active, not recruiting <b>Location(s)</b> : 6 EU countries, Canada, United States, Australia and the Republic of Korea. <b>Study completion date</b> : May 2022
<b>Trial design</b>	Randomised, parallel assignment, open label.
<b>Population</b>	N = 400; Chronic AD and history of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable, aged 12 years and older
<b>Intervention(s)</b>	Induction Period (baseline-week 16): Two SC injections of lebrikizumab as a loading dose at baseline and week 2 visits followed by a single injection every 2 weeks (Q2W) from week 4 until week 14. Maintenance Period:

	<ul style="list-style-type: none"> <li>- Treatment from week 16 to week 52 is based on re-randomisation of responders in the Induction Period. Participants re-randomised to lebrikizumab Q2W arm receive two lebrikizumab injections Q2W</li> <li>- Treatment from week 16 to week 52 is based on re-randomisation of responders in the Induction Period. Participants re-randomised to lebrikizumab Q4W arm receive one lebrikizumab injection Q4W, with one placebo injection 2 weeks after each lebrikizumab injection.</li> </ul>
<b>Comparator(s)</b>	Matched placebo
<b>Outcome(s)</b>	<p>Primary outcomes;</p> <ul style="list-style-type: none"> <li>- Percentage of participants with an IGA score of 0 or 1 and a reduction <math>\geq 2</math> points from Baseline to week 16 [Time frame: baseline to week 16]</li> <li>- Percentage of participants achieving EASI-75 (<math>\geq 75\%</math> reduction in EASI score) from Baseline to week 16 [Time frame: baseline to week 16]</li> </ul> <p>See trial record for full list of other outcomes.</p>
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<p><b>ADvocate2</b>, <a href="#">NCT04178967</a>, <a href="#">2019-002933-12</a>; A Randomized, Double-blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab in Patients With Moderate to Severe Atopic Dermatitis.  <b>Phase III</b> - Active, not recruiting  <b>Location(s)</b>: 2 EU countries, Canada, United States and other countries.  <b>Study completion date</b>: June 2022</p>
<b>Trial design</b>	Randomised, parallel assignment, open label.
<b>Population</b>	N = 400; Chronic AD and history of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable, aged 12 years and older
<b>Intervention(s)</b>	<p>Induction Period (baseline-week 16): Two SC injections of lebrikizumab as a loading dose at baseline and week 2 visits followed by a single injection Q2W from week 4 until week 14.</p> <p>Maintenance Period:</p> <ul style="list-style-type: none"> <li>- Treatment from week 16 to week 52 is based on re-randomisation of responders in the Induction Period. Participants re-randomised to Lebrikizumab Q2W arm receive two lebrikizumab injections Q2W.</li> <li>- Treatment from week 16 to week 52 is based on re-randomisation of responders in the Induction Period. Participants re-randomised to Lebrikizumab Q4W arm receive one lebrikizumab injection Q4W, with one placebo injection 2 weeks after each lebrikizumab injection.</li> <li>- Escape arm</li> </ul>
<b>Comparator(s)</b>	Matched placebo
<b>Outcome(s)</b>	<p>Primary outcomes;</p> <ul style="list-style-type: none"> <li>- Percentage of participants with an IGA score of 0 or 1 and a reduction <math>\geq 2</math> points from Baseline to Week 16 [Time frame: baseline to week 16]</li> </ul>

	<ul style="list-style-type: none"> <li>- Percentage of participants achieving EASI-75 (<math>\geq 75\%</math> reduction in EASI score) from baseline to week 16 [Time frame: baseline to week 16 ]</li> </ul> <p>See trial record for full list of other outcomes.</p>
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<b>ADjoin, <a href="#">NCT04392154</a>, <a href="#">2020-001211-24</a></b> ; A Long-term Study to Assess the Safety and Efficacy of Lebrikizumab in Patients With Moderate-to-Severe Atopic Dermatitis (ADjoin) <b>Phase III - Recruiting</b> <b>Location(s):</b> 10 EU countries, Canada, United States, and other countries. <b>Primary completion date:</b> May 2024
<b>Trial design</b>	Non-randomised, parallel assignment, double-blind
<b>Population</b>	N = 1000 (estimated); received treatment in a lebrikizumab study, NCT04146363, NCT04178967, NCT04250337, NCT04250350, NCT04178967 and have adequately completed the study treatments and last patient visit of the parent trial; aged 12 years or older
<b>Intervention(s)</b>	Experimental arms: <ul style="list-style-type: none"> <li>- lebrikizumab Q2W arm will receive investigational product Q2W by SC injection</li> <li>- lebrikizumab Q2W arm will receive investigational product Q2W by SC injection. Some participants will receive loading doses</li> <li>- Open-Label Addendum will receive lebrikizumab Q2W by SC injection after loading doses</li> <li>- lebrikizumab Q4W arm will receive investigational product Q4W by SC injection</li> </ul>
<b>Comparator(s)</b>	Lebrikizumab balanced with placebo to maintain the blind between treatment arms
<b>Outcome(s)</b>	Primary outcome; <ul style="list-style-type: none"> <li>- Percentage of participants discontinued from study treatment due to adverse events through the last treatment visit [Time frame: baseline to week 100]</li> </ul> <p>See trial record for full list of other outcomes.</p>
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<b>ADore, <a href="#">NCT04250350</a>, <a href="#">2019-004301-28</a></b> ; An Open-Label, Single-Arm Study to Assess the Safety and Efficacy of Lebrikizumab in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis <b>Phase III - Active, not recruiting</b> <b>Location(s):</b> Australia, Canada, Poland, United States <b>Study completion date:</b> July 2022
<b>Trial design</b>	Single group assignment, open-label
<b>Population</b>	N = 200; Chronic AD (according to American Academy of Dermatology Consensus Criteria), history of inadequate response to treatment with topical medications; aged 12 to 17 years
<b>Intervention(s)</b>	Lebrikizumab SC injection Q2W
<b>Comparator(s)</b>	None

<b>Outcome(s)</b>	Primary outcome; <ul style="list-style-type: none"> <li>- Percentage of participants discontinued from study treatment due to adverse events [Time frame: baseline to week 52]</li> </ul> <p>See trial record for full list of other outcomes.</p>
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<b>J2T-DM-KGAF; <a href="#">NCT03443024</a></b> ; A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Efficacy and Safety of Lebrikizumab in Patients With Moderate-to-Severe Atopic Dermatitis <b>Phase II - Completed</b> <b>Location(s):</b> United States <b>Study completion date:</b> May 2019
<b>Trial design</b>	Randomised, parallel assignment, double-blind.
<b>Population</b>	N = 280; Chronic AD as defined by Hanifin and Rajka (1980) that has been present for $\geq 1$ year before the screening visit; aged 18 years or older
<b>Intervention(s)</b>	Experimental arms: <ul style="list-style-type: none"> <li>- 125 mg Lebrikizumab administered SC once every 4 weeks (Q4W)</li> <li>- 250 mg Lebrikizumab administered SC once Q4W</li> <li>- 250 mg Lebrikizumab administered SC once Q2W</li> </ul>
<b>Comparator(s)</b>	Placebo administered SC once Q2W
<b>Outcome(s)</b>	Primary outcome; <ul style="list-style-type: none"> <li>- Percent change from baseline in eczema area and severity index (EASI) [Time frame: baseline week 16]</li> </ul> <p>See trial record for full list of other outcomes.</p>
<b>Results (efficacy)</b>	<ul style="list-style-type: none"> <li>- Compared with placebo (EASI least squares mean [SD] percentage change, -41.1% [56.5%]), lebrikizumab groups showed dose-dependent, statistically significant improvement in the primary end point vs placebo at week 16: 125 mg every 4 weeks (-62.3% [37.3%], <math>P = .02</math>), 250 mg every 4 weeks (-69.2% [38.3%], <math>P = .002</math>), and 250 mg every 2 weeks (-72.1% [37.2%], <math>P &lt; .001</math>).</li> <li>- Differences vs placebo-treated patients (2 of 44 [4.5%]) in pruritus NRS improvement of at least 4 points were seen as early as day 2 in the high-dose lebrikizumab group (9 of 59 [15.3%]).<sup>25</sup></li> </ul>
<b>Results (safety)</b>	<ul style="list-style-type: none"> <li>- Treatment-emergent adverse events were reported in 24 of 52 placebo patients (46.2%) and in lebrikizumab patients as follows: 42 of 73 (57.5%) for 125 mg every 4 weeks, 39 of 80 (48.8%) for 250 mg every 4 weeks, and 46 of 75 (61.3%) for 250 mg every 2 weeks; most were mild to moderate and did not lead to discontinuation.</li> <li>- Low rates of injection-site reactions (1 of 52 [1.9%] in the placebo group vs 13 of 228 [5.7%] in all lebrikizumab groups), herpesvirus infections (2 [3.8%] vs 8 [3.5%]), and conjunctivitis (0% vs 6 [2.6%]) were reported.<sup>25</sup></li> </ul>

## ESTIMATED COST

The cost of lebrikizumab is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal in development. Tralokinumab for treating moderate to severe atopic dermatitis in people aged 12 and over (ID3823). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Upadacitinib for treating moderate to severe atopic dermatitis in people aged 12 and over (ID3733). Expected date of issue to be confirmed.
- NICE technology appraisal. Baricitinib for treating moderate to severe atopic dermatitis (TA681). March 2021.
- NICE technology appraisal. Dupilumab for treating moderate to severe atopic dermatitis (TA534). August 2018.

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Dermatology Services (All Ages). A12/S/a/.

### OTHER GUIDANCE

- Journal of the European Academy of Dermatology and Venereology. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. 2018.<sup>26</sup>
- Scottish Intercollegiate Guidelines Network. Management of atopic eczema in primary care (SIGN 125). 2011.<sup>27</sup>

## ADDITIONAL INFORMATION

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