

## HEALTH TECHNOLOGY BRIEFING NOVEMBER 2020

### Tezepelumab for severe, uncontrolled asthma

<b>NIHRIO ID</b>	11732	<b>NICE ID</b>	10311
<b>Developer/Company</b>	AstraZeneca UK Ltd	<b>UKPS ID</b>	654753

<b>Licensing and market availability plans</b>	Currently in phase III clinical trials
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### SUMMARY

Tezepelumab, as an add-on to current therapy, is in clinical development for the treatment of children and adults over 12 years old, with severe, uncontrolled asthma. Asthma is a common lung condition that causes wheezing, coughing and breathlessness. Individuals with asthma can suffer an asthma attack, which in severe cases can be fatal. Patients with severe asthma have ongoing daily symptoms despite high-intensity asthma treatment. Therefore, there is need for personalised treatment strategies which include a need for biological therapies which can specifically target the cause of an individual's asthma.

Tezepelumab is a monoclonal antibody (protein) that targets proteins early in the inflammatory cascade. By targeting proteins early in the inflammatory cascade, several downstream inflammatory proteins are suppressed, thereby decreasing inflammation. Tezepelumab given as an add-on-therapy to patients with severe uncontrolled asthma has been shown to be safe, well tolerated, and effective. Tezepelumab is administered subcutaneously. If licensed, tezepelumab as an add on therapy would offer an additional biological therapy to those over 12 years old, with severe asthma.

## PROPOSED INDICATION

Treatment of adults and adolescents with severe, uncontrolled asthma.<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Tezepelumab (MEDI19929) is a potential first-in-class medicine blocking thymic stromal lymphopoietin (TSLP), an epithelial cytokine, critical in the initiation and persistence of airway inflammation. Blocking TSLP may prevent the release of pro-inflammatory cytokines by immune cells resulting in the prevention of asthma exacerbations and improved asthma control. Due to its activity early in the inflammation cascade, tezepelumab may be suitable for a broad population of patients with severe, uncontrolled asthma, irrespective of patient phenotype including type 2 (T2) biomarker status.<sup>2</sup>

In a phase II clinical trial (NCT02054130), participants received either 70mg or 210mg tezepelumab subcutaneously once every four weeks from day one to week forty-eight along with subcutaneous placebo once every four weeks from week two to week fifty. In addition, one arm of patients received 280mg tezepelumab subcutaneously once every two weeks from day one to week fifty.<sup>1</sup> In the phase III trial NAVIGATOR (NCT03347279) patients were administered 210mg tezepelumab once every four weeks.<sup>3</sup>

### INNOVATION AND/OR ADVANTAGES

Tezepelumab is a first-in-class human monoclonal antibody. Tezepelumab given as an add-on-therapy to patients with severe uncontrolled asthma has shown safety, tolerability and efficacy in trials undertaken to date.<sup>4</sup>

In September 2018, tezepelumab was awarded Breakthrough Therapy Designation by the Food and Drug Administration (FDA) for patients with severe asthma without an eosinophilic phenotype based on the tezepelumab Phase IIb (PATHWAY) data that showed a significant reduction in the annual asthma exacerbation rate compared with placebo in a broad population of severe asthma patients irrespective of patient phenotype including T2 biomarker status.<sup>5</sup> Currently available biologic therapies only target T2-driven inflammation. Tezepelumab is a potential first-in-class new medicine that blocks TSLP - an upstream modulator of multiple inflammatory pathways.<sup>2</sup>

In the phase II trial PATHWAY (NCT02054130) the use of tezepelumab at a dose of 70 mg every 4 weeks (low dose; 145 patients), 210 mg every 4 weeks (medium dose; 145 patients), or 280 mg every 2 weeks (high dose; 146 patients) resulted in annualised asthma exacerbation rates at week 52 of 0.26, 0.19, and 0.22, respectively, as compared with 0.67 in the placebo group (148 patients). Thus, exacerbation rates in the respective tezepelumab groups were lower by 61%, 71%, and 66% than the rate in the placebo group ( $P < 0.001$  for all comparisons).<sup>6</sup> The incidence of adverse events (~60%) was similar across all treatment groups.<sup>7</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tezepelumab is not currently licensed in the EU/UK for any other indication.

Tezepelumab is currently in phase II/III clinical development for the treatment of asthma, atopic dermatitis and chronic obstructive pulmonary disease (COPD).<sup>8</sup>

In the phase IIb study (PATHWAY), the most common adverse events were asthma-related, nasopharyngitis, headaches and bronchitis.<sup>2</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

Asthma is a common lung condition that causes occasional breathing difficulties. Symptoms include wheezing, breathlessness, a tight chest and coughing.<sup>9</sup> Many things can cause these symptoms, but they are more likely if they: happen often and keep coming back; are worse at night and early in the morning; seem to happen in response to an asthma trigger (cold and flu, exercise, allergy, smoke, medicines, emotions, weather, mould or damp etc.).<sup>10,11</sup>

The symptoms can get temporarily worse; this is known as an asthma attack. Signs of a severe asthma attack include wheezing; coughing; chest tightness becoming severe and constant; breathlessness; breathing faster; fast heart rate; drowsiness, confusion, exhaustion, or dizziness; blue lips or fingers; and fainting.<sup>10</sup>

The exact cause of asthma is unknown. People with asthma have swollen (inflamed) and sensitive airways that become narrow and clogged with sticky mucus in response to certain triggers. Genetics, pollution, and modern hygiene standards have been suggested as causes, but there is not currently enough evidence to know if any of these do cause asthma. Risk factors associated with asthma are: having an allergy related condition (eczema, food allergy, hay fever); having a family history of asthma or atopic conditions; having had bronchiolitis; exposure to tobacco smoke as a child; your mother smoking during pregnancy; being born prematurely (before 37 weeks) or with a low birth weight.<sup>11</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

Asthma affects 334 million people worldwide. Up to 10% of asthma patients have severe asthma, which may be uncontrolled despite high doses of standard-of-care asthma controller medicines and can require the use of chronic oral corticosteroids (OCS). Severe uncontrolled asthma is debilitating and potentially fatal with patients experiencing frequent exacerbations and significant limitations on lung function and quality of life.<sup>2</sup>

In the UK, 5.4 million people are currently receiving treatment for asthma: 1.1 million children (1 in 11) and 4.3 million adults (1 in 12). In England, 4.5 million people are currently receiving treatment for asthma (932,000 children and 3,600,000 adults). Around 200,000 people in the UK have severe asthma; this is a debilitating form of the condition that does not respond to usual treatments.<sup>12</sup>

In England 2017/2018 there were 102,408 finished consultant episodes (FCE) and 73,877 hospital admissions with a primary diagnosis of asthma (ICD-10 code J45), resulting in 148,548 FCE bed days and 11,700 day cases.<sup>13</sup> In England in 2017 there were 1,156 deaths with asthma (ICD-10 codes J45-J46) recorded as the underlying cause.<sup>14</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

There is no cure for asthma, therefore treatment aims to control symptoms so that asthma patients are able to have normal functionality whilst minimising adverse reactions to the

treatment. Patients normally complete a personal action plan with their doctor or specialist asthma nurse. The personal action plan focusses on which medicines to take and adherence to regime, how to identify if asthma symptoms are getting worse and what to do if an acute asthma exacerbation occurs.<sup>15</sup>

Current guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment aligned with the pathway of Global Initiatives of Asthma (GINA).<sup>16</sup> If asthma symptoms are not under control, then the treatment should be increased to the next step. If asthma symptoms are under control, then treatment should be stepped down until the patient reaches a point where their asthma is under control at the lowest possible controlling therapy.<sup>17</sup>

## CURRENT TREATMENT OPTIONS

Severe asthma is asthma that is the most difficult to control so, although it can be treated, it can take time to find a combination of medicines that work. People with severe asthma may be prescribed the same medicines as people without severe asthma, but often at higher doses.<sup>18</sup>

Patients with severe asthma are prescribed:<sup>18</sup>

- A prevention inhaler (corticosteroids)
- A relief inhaler

Add on treatments may include:<sup>18,19</sup>

- Long-acting bronchodilators (LABAs)
- Leukotriene receptor agonists (LTRAs)
- Slow-release theophylline
- Beta-2 agonist tablets
- Long-acting muscarinic receptor agonists (LAMAs)

If symptoms persist, patients may be prescribed daily steroids or biological therapies (benralizumab, omalizumab, mepolizumab, reslizumab).<sup>18</sup>

Several complementary therapies have been suggested as possible treatments for asthma including:<sup>15</sup>

- Breathing exercises
- Traditional Chinese herbal medicine
- Acupuncture
- Ionisers
- Manual therapies (e.g. chiropractic)
- Homeopathy
- Dietary supplements

There is little evidence to suggest many of these treatments help.<sup>15</sup>

## PLACE OF TECHNOLOGY

If licensed, tezepelumab would offer an additional treatment option for adolescents and adults with severe, uncontrolled asthma.<sup>1</sup>

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	<b>NAVIGATOR</b> <a href="#">NCT03347279</a> , A Multicentre, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults and Adolescents With Severe Uncontrolled Asthma <b>Phase III</b> – active, not recruiting <b>Locations:</b> EU (incl. UK), US and other countries <b>Primary completion date:</b> December 2020
<b>Trial design</b>	Randomised, parallel assignment, placebo-controlled
<b>Population</b>	N=1061; children and adults aged 12 years to 80 years; diagnosed with asthma for at least 12 months; received asthma controller medication with medium or high dose inhaled corticosteroids (ICS) for at least 12 months
<b>Intervention(s)</b>	Tezepelumab subcutaneous injection
<b>Comparator(s)</b>	Matched placebo
<b>Outcome(s)</b>	Annualised asthma exacerbation rate (AERR) [Time frame: Baseline to week 52]  For full list of outcomes, see trial record
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<b>SOURCE</b> <a href="#">NCT032406078</a> , A Multicentre, Randomized, Double-Blind, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults With Oral Corticosteroid Dependent Asthma <b>Phase III</b> – completed <b>Locations:</b> Europe (excl. UK), US and other countries <b>Study completion date:</b> September 2020
<b>Trial design</b>	Randomised, parallel assignment, placebo-controlled
<b>Population</b>	N=150; adults aged 18 to 80 years with asthma; prescribed medium or high dose ICS for at least 12 months
<b>Intervention(s)</b>	Tezepelumab 210mg subcutaneous injection every four weeks <sup>20</sup>
<b>Comparator(s)</b>	Matched placebo
<b>Outcome(s)</b>	Categorised percent reduction from baseline in the daily OCS dose while not losing asthma control [Time frame: week 48]  For full list of outcomes, see trial record
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<b>PATHWAY</b> , <a href="#">NCT02054130</a> , A Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI9929 in Adult Subjects With Inadequately Controlled, Severe Asthma <b>Phase II</b> – Completed <b>Locations:</b> Europe (excl. UK), US and other countries <b>Study completion date:</b> March 2017
<b>Trial design</b>	Randomised, parallel assignment, placebo-controlled
<b>Population</b>	N=584; adults aged 18 to 75 years; diagnosed asthma; medium or high dose ICS plus long acting beta-2 agonist
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>– Tezepelumab 70mg subcutaneously once every four weeks from day one to week forty-eight along with subcutaneous placebo once every four weeks from week two to week fifty</li> <li>– Tezepelumab 210mg subcutaneously once every four weeks from day one to week forty-eight along with subcutaneous placebo once every four weeks from week two to week fifty</li> <li>– Tezepelumab 280mg subcutaneously once every two weeks from day one to week fifty</li> </ul>
<b>Comparator(s)</b>	Placebo matched to tezepelumab once every two weeks from day one to week fifty
<b>Outcome(s)</b>	Annualised asthma exacerbation rate (AERR) [Time frame: baseline to week 52]  For full list of outcomes, see trial record
<b>Results (efficacy)</b>	The use of tezepelumab at a dose of 70 mg every 4 weeks (low dose; 145 patients), 210 mg every 4 weeks (medium dose; 145 patients), or 280 mg every 2 weeks (high dose; 146 patients) resulted in annualised asthma exacerbation rates at week 52 of 0.26, 0.19, and 0.22, respectively, as compared with 0.67 in the placebo group (148 patients). Thus, exacerbation rates in the respective tezepelumab groups were lower by 61%, 71%, and 66% than the rate in the placebo group (P<0.001 for all comparisons). Similar results were observed in patients regardless of blood eosinophil counts at enrolment. The prebronchodilator forced expiratory volume in 1 second at week 52 was higher in all tezepelumab groups than in the placebo group (difference, 0.12 litres with the low dose [P=0.01], 0.11 litres with the medium dose [P=0.02], and 0.15 litres with the high dose [P=0.002]). A total of 2 patients in the medium-dose group, 3 in the high-dose group, and 1 in the placebo group discontinued the trial regimen because of adverse events <sup>6</sup>
<b>Results (safety)</b>	The incidence of adverse events (~60%) was similar across all treatment groups <sup>7</sup>

## ESTIMATED COST

The cost of tezepelumab is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal guidance. Benralizumab for treating severe eosinophilic asthma (TA565) March 2019
- NICE technology appraisal guidance. Reslizumab for treating severe eosinophilic asthma (TA479) October 2017
- NICE technology appraisal guidance. Mepolizumab for treating severe refractory eosinophilic asthma (TA431) January 2017
- NICE technology appraisal guidance. Omalizumab for treating severe persistent allergic asthma. (TA278). April 2013.
- NICE technology appraisal guidance. Inhaled corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over. (TA138). March 2008.
- NICE technology appraisal guidance. Inhaler devices for routine treatment of chronic asthma in older children (aged 5-15 years). (TA38). March 2002.
- NICE interventional procedures guidance. Bronchial thermoplasty for severe asthma. (IPG635). December 2018.
- NICE guidance. COVID-19 rapid guideline: severe asthma. (NG166). April 2020.
- NICE guidance. Asthma: diagnosis, monitoring and chronic asthma management. (NG80). November 2017.

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Specialised Respiratory Services (Adult) – Severe Asthma. 170002/S. April 2017.

### OTHER GUIDANCE

- Scottish Intercollegiate Guidance Network (SIGN). British guideline on the management of asthma. July 2019.<sup>21</sup>
- Interventional European Respiratory Society, American Thoracic Society. Guidelines on the definition, evaluation and treatment of severe asthma. April 2014.<sup>22</sup>

## ADDITIONAL INFORMATION

## REFERENCES

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