Alpha-1 antitrypsin (Respreeza) for emphysema associated with alpha-1 antitrypsin deficiency – maintenance therapy

SUMMARY

Respreeza (alpha-1 antitrypsin, Zemaira) is intended to be used as maintenance therapy for the treatment of emphysema associated with alpha-1 antitrypsin deficiency. If licensed, it will offer a novel treatment option for patients with congenital alpha-1 antitrypsin deficiency emphysema who currently have no targeted therapies available. Respreeza is an alpha-1 proteinase inhibitor, which inhibits neutrophil elastase and other proteases in the lower respiratory tract. Respreeza does not currently have Marketing Authorisation in the EU for any indication.

The prevalence of the genotype associated with severe alpha-1 antitrypsin deficiency is estimated to be 1 in every 1,600 to 5,000 newborns. Using and applying data from a local registry (ADAPT), it is estimated that 670 patients in England have alpha-1 antitrypsin deficiency. According to the registry, approximately 80% of identified patients have clinically significant disease which may require therapy with Respreeza; in England, this would equate to a population of 540 patients. The number of people with alpha-1 antitrypsin deficiency who go on to develop emphysema is unknown, but it is thought that the majority remain unaffected.

There are no specific licensed treatment options for emphysema associated with congenital alpha-1 antitrypsin deficiency. Treatment options for alpha-1 antitrypsin related lung disease do not differ from standard treatment of chronic obstructive pulmonary disease, and include long-acting inhaled bronchodilators, inhaled corticosteroids, mucolytic agents, antibiotics, systemic steroids, and supplemental oxygen for specific cases. Respreeza has completed two phase III trials comparing its effect on lung density against treatment with placebo. These trials reported in 2013 and 2014.
TARGET GROUP

- Emphysema associated with congenital alpha-1 antitrypsin deficiency: moderate to severe airflow obstruction defined as FEV$_1^a$ $\geq$25% and $\leq$80% predicted – maintenance augmentation therapy.

TECHNOLOGY

DESCRIPTION

Respreeza (alpha-1 antitrypsin, Zemaira) is a highly purified and stable human alpha-1 proteinase inhibitor, which inhibits neutrophil elastase and other proteases in the lower respiratory tract. Respreeza is intended for the treatment of emphysema in patients with congenital alpha-1 antitrypsin (A1AT) deficiency. Respreeza is administered by intravenous (IV) infusion at 60mg/kg, once weekly until a serum alpha-1 proteinase inhibitor levels over 11µM are achieved.

Respreeza does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, Respreeza will offer a novel treatment option for patients with emphysema as a result of congenital A1AT deficiency who currently have no targeted and non-surgical therapies available.

DEVELOPER

CSL Behring Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Completed phase III clinical trials.

PATIENT GROUP

BACKGROUND

A1AT is a protein predominantly produced by hepatocytes and released into the bloodstream by the liver. It is found in all body tissues, but appears to have primary physiologic significance in the lungs, protecting alveolar tissue from damage by enzymes such as neutrophil elastase, cathepsin G and proteinase 3\textsuperscript{1,2}. A1AT deficiency is a rare, autosomal recessive genetic disorder defined by reduced serum concentration of A1AT and/or identification of a defective protein phenotype or genotype\textsuperscript{3,4}. Levels of proteins circulating in the blood vary depending on the presence of various medical conditions and the health of an individual. Normal serum concentration ranges between 1.5 and 3.5g/l (or 20 to 48µM)\textsuperscript{1} and a serum concentration of below 0.5g/l (11µM) often requires further analysis\textsuperscript{1}.

\textsuperscript{a} Forced expiratory volume in 1 second.
Located on chromosome 14, the SERPINA1 gene (previously known as proteinase inhibitor [PI] gene) encodes the A1AT protein, and over 100 allelic gene variants have been described, each classified according to effects on levels of serum A1AT protein levels. Four main categories of alleles have been identified: normal alleles producing normal serum concentrations of A1AT and functional proteins; dysfunctional alleles; deficient alleles; and null alleles producing no proteins and thus undetectable serum levels of A1AT. Dysfunctional alleles have been associated with the production of proteins which lead to both normal and abnormal A1AT serum concentrations. Deficient alleles produce a defective protein causing decreased liver secretion of A1AT and low serum levels. A1AT deficiency and/or dysfunction are associated with an imbalance in protease-antiprotease activity leading to tissue proteolysis, and thus, leading to emphysema. Variants of A1AT proteins are also classified based on electrophoresis gel movements; Z-very slow, S-slow, M-medium (resulting in normal levels of A1AT), and F-fast. Development of disease is seen with null variants or genotypes resulting in impaired gene expression, translation or protein synthesis. Patients with disease are usually homozygous (ZZ or SS phenotypes) or heterozygous (MS, MZ, or SZ phenotypes) for Z or S alleles.

Symptoms of A1AT deficiency are due to the manifestations of the deficiency, i.e. emphysema, and include persistent breathlessness, wheezing, cough and exacerbation of disease. The development, progression and manifestations of chronic obstructive pulmonary disease (COPD) vary considerably in patients with A1AT deficiency, suggesting that disease expression may not solely be genetic, but additionally linked to environmental exposures. Besides emphysema, A1AT deficiency has associations with liver disease, panniculitis, vasculitis, asthma, pancreatitis, and aneurysms of the abdominal aorta and brain arteries.

Though emphysema due to A1AT deficiency is considered to be largely congenital, symptoms rarely develop before the age of 20 and are more commonly reported in patients over the age of 40. People who smoke are at increased risk of developing early onset COPD in the presence of A1AT deficiency. In non-smokers, COPD symptoms usually develop in people 50 years of age and above. Severe exacerbations can lead to increasing lung function decline and thus can severely reduce a patients’ quality of life. The second largest cause of emergency admissions in the UK is COPD, with one in eight emergency admissions to hospital occurring as a result of COPD, and accounting for more than £800 million in direct healthcare costs.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

The prevalence of the genotype associated with severe A1AT deficiency is estimated to be 1 in every 1,600 to 5,000 newborns. A patient registry (ADAPT) for A1AT deficiency has 69 patients registered from the West Midlands. If replicated in all regions, this would suggest a total of approximately 670 patients in England (using the upper estimate). The ADAPT registry also indicates that approximately 80% of identified patients have clinically significant disease which may be eligible for therapy with Respreeza; this equates to a population of up to 540 patients in England. However, the number eligible for treatment may be greater, as many patients remain undiagnosed.

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b COPD is now the preferred term for the conditions in patients with airflow obstruction who were previously diagnosed as having chronic bronchitis or emphysema.
The number of people with A1AT deficiency who go on to develop emphysema is not known, but it is thought that the majority remain unaffected\(^5\). In the UK, approximately 900,000 people present with COPD, and an additional 2 million people are thought to have COPD, but remain undiagnosed\(^1^1\). The prevalence of COPD in England is estimated at 1.6%, equating to a current population of 861,853\(^1^2,1^3\).

There were 716 hospital admissions in 2012-13 in England from disorders of plasma-protein metabolism, not elsewhere classified (ICD-10 E88.0), resulting in 922 finished consultant episodes and 3,104 bed days\(^1^4\). In 2012, there were 54 deaths from A1AT deficiency registered in England and Wales\(^1^5\).

### PATIENT PATHWAY

### RELEVANT GUIDANCE

#### NICE Guidance

- NICE interventional procedures guideline in development. Insertion of endobronchial nitinol coils to improve lung function in emphysema. Expected date of issue to be confirmed.

#### Other Guidance

- Institute for Clinical Systems Improvement. Diagnoses and management of chronic obstructive pulmonary disease (COPD). 2013\(^1^6\).
- Thorax. Guideline for non-CF Bronchiectasis. 2010\(^1^7\).

### CURRENT TREATMENT OPTIONS

There are no specific licensed treatment options for A1AT deficiency, however there are four potential treatment approaches which are under investigation: 1) IV human plasma-derived A1AT augmentation therapy, 2) augmentation therapy by inhalation, 3) recombinant A1AT augmentation therapy, and 4) synthetic elastase inhibition\(^2\). Several guidelines exist for the treatment of COPD\(^1^1,1^8,1^9,2^0\). Treatment options for A1AT related lung disease do not differ from standard treatment of COPD and include\(^1,2,4,1^8\):

- Long-acting inhaled bronchodilators.
- Inhaled corticosteroids.
- Mucolytic agents.
- Antibiotics and systemic steroids – during exacerbations.
- Supplementary oxygen – portable oxygen cylinders in patients experiencing desaturation during exercise and long-term oxygen therapy for patients with severe hypoxaemia.
- Pulmonary rehabilitation – for patients with functional impairment.
- Lung transplantation – considered for selected individuals with severe functional impairment and airflow obstruction.

Additionally, annual influenza vaccination and pneumococcal vaccination every five years is recommended for A1AT deficiency emphysema\(^1\). Lung volume reduction surgery may also be considered in patients with emphysema, however the evidence-base for its efficacy in patients with A1AT deficiency emphysema is lacking and inconsistent\(^2,18\).

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00261833, CE1226_4001, 1449, 2005-003459-12, RAPID; A1AT vs placebo; phase III/IV.</th>
<th>NCT00670007, CE1226_3001, 1466, 2007-007129-38, RAPID extension study; A1AT vs placebo; phase III/IV.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>CSL Behring.</td>
<td>CSL Behring.</td>
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<td>Status</td>
<td>Published in abstract.</td>
<td>Published in abstract.</td>
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<tr>
<td>Source of information</td>
<td>Abstract(^21), trial registry(^22).</td>
<td>Abstract(^23), trial registry(^24).</td>
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<tr>
<td>Location</td>
<td>EU (not UK), USA, Canada, Australia and Russia.</td>
<td>EU (not UK), Canada and Australia.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Uncontrolled, single arm.</td>
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<tr>
<td>Participants</td>
<td>n=180 (A1AT, n=93; placebo, n=87); aged 18 to 65 years; diagnosed alpha-1-proteinase inhibitor deficiency (serum levels &lt;111µM or &lt;80mg/dL); emphysema and FEV(_1) (\geq)35% and (\leq)70% predicted; no infection with hepatitis A, B or C, or HIV.</td>
<td>n=140 (planned); aged 18 years and older; completed 2 year treatment and observation period in the RAPID trial. A1AT patients from RAPID trial known as Early-Start cohort, placebo group from RAPID trial known as Delayed-Start cohort.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to 60mg/kg A1AT or placebo, both IV and once weekly.</td>
<td>All participants received 60mg/kg A1AT, IV, once weekly.</td>
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<td>Follow-up</td>
<td>Active treatment period and follow-up period 2 years.</td>
<td>Active treatment period and follow-up period up to 2 years.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Change in lung density.</td>
<td>Change in lung density.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Number of pulmonary exacerbations; FEV(_1); time to first pulmonary exacerbation; change in lung density; exercise capacity; quality of life assessed with SGRQ(^c); adverse events (AEs); FEV(_1), % predicted; FEV(_1)/FVC(^d) ratio; diffusion capacity for carbon monoxide; characteristics of pulmonary exacerbations.</td>
<td>Number of pulmonary exacerbations; FEV(_1); change in lung density; SGRQ; FEV(_1)/FVC; annual rate of pulmonary exacerbations; time to first onset of pulmonary exacerbation.</td>
</tr>
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<td>Key results</td>
<td>Annual rate of lung density loss (g/L), -1.45 for A1AT group, and -2.19 for placebo (difference 0.74, p=0.017). Secondary outcome variables were reportedly not significantly different between groups.</td>
<td>Interim results. Annual rate of lung density loss (g/L), -1.06 for Early-Start cohort and -0.97 for Delayed-Start cohort (difference -0.095, 95%CI, -1.08 to 0.89)</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>AEs not significantly different between groups. Deaths: 1 in A1AT group and 3 in placebo group.</td>
<td>Not reported.</td>
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</table>

\(^c\) St George's Respiratory Questionnaire.

\(^d\) Forced vital capacity.
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<th>Expected reporting date</th>
<th>Study completion date reported as September 2012.</th>
<th>Study completion date reported as September 2014.</th>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of Respreeza is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Other: improved quality of life for patients and carers.
- Reduced symptoms or disability
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services: requirement for new facilities, regular IV infusions.
- Decreased use of existing services: if effective, potential for reduced use of secondary care/specialist services.
- Re-organisation of existing services
- Need for new services
- Other: None identified

**Impact on Costs and Other Resource Use**

- Increased drug treatment costs: uncertain and additional unit cost compared to existing treatments
- Reduced drug treatment costs
- Other increase in costs: additional costs for IV administration in clinic
- Other reduction in costs: if effective, potential for reduced use of secondary care/specialist services.
- Other: None identified

**Other Issues**

- Clinical uncertainty or other research question identified: None identified

**REFERENCES**