Anti-\textit{Pseudomonas aeruginosa} IgY for pseudomonal infection in cystic fibrosis

\textbf{LAY SUMMARY}

Cystic fibrosis is a long-term condition which affects the lungs and digestive system. The lungs can become clogged with thick, sticky mucus, which can cause problems with breathing from a young age. Over many years, the lungs become increasingly damaged and may eventually stop working properly. \textit{Pseudomonas aeruginosa} is a bacterium that can damage the lungs of patients with cystic fibrosis even more, it can be difficult to treat, and once it becomes well-established, it may never be properly cleared from the lung.

\textit{Anti-\textit{Pseudomonas aeruginosa}} IgY is a new drug for the treatment of infection with \textit{Pseudomonas aeruginosa} in patients with cystic fibrosis. It is gargled like a mouthwash once a day. If \textit{Anti-\textit{Pseudomonas aeruginosa}} IgY is licensed for use in the UK, it could be a new treatment option for patients with cystic fibrosis that may help prevent the bacteria from getting to the lungs and improve quality of life.

\textbf{NIHR HSRIC ID: 3707}
**TARGET GROUP**


**TECHNOLOGY**

**DESCRIPTION**

Anti-*Pseudomonas aeruginosa* IgY is an avian polyclonal IgY antibody directed against *Pseudomonas aeruginosa* that is intended for the prevention and treatment of cystic fibrosis-associated respiratory tract infections. The solution, produced from hens’ eggs, contains antibodies which attack the flagella of bacteria, preventing them from attaching to respiratory epithelia cell walls of the patients’ mouth and throat, stopping further infection of the lower airways. In phase III clinical trials, anti-*Pseudomonas aeruginosa* IgY is gargled orally at 50mg once daily.  

Anti-*Pseudomonas aeruginosa* IgY does not currently have Marketing Authorisation in the EU for any indication.

**INNOVATION and/or ADVANTAGES**

If licensed, anti-*Pseudomonas aeruginosa* IgY will offer an additional treatment option for patients with cystic fibrosis to prevent pulmonary infections caused by *Pseudomonas aeruginosa*. The developer states that anti-*Pseudomonas aeruginosa* IgY is intended to be used as an ‘add-on’ treatment in addition to regular cystic fibrosis medication to prevent *Pseudomonas aeruginosa* infection, delay the occurrence of a chronic infection and reduce the amount of antibiotics required, which in turn leads to improved prognosis.

**DEVELOPER**

Mukoviszidose Institut gGmbH (sponsor of clinical trial NCT01455675).  
Collaborators include: Cork University, Ireland; Uppsala University, Sweden; Clinic of Paediatric Respiratory Disease, Belgium; and 40 other active study sites within the EU.

**AVAILABILITY, LAUNCH OR MARKETING**

Anti-*pseudomonas aeruginosa* IgY is a designated orphan drug in the EU.

In phase III clinical trials.

**PATIENT GROUP**

**BACKGROUND**

Cystic fibrosis is the most common life-limiting, autosomal recessively inherited disease in people from White ethnic groups. The underlying cause of cystic fibrosis is the loss of epithelial chloride transport due to mutations in the cystic fibrosis transmembrane

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a Developer provided information.
conductance regulator (CFTR) gene which encodes the CFTR protein. Normally, CFTR is present at the epithelial cell surface where it allows chloride transport across the epithelial cell membrane to maintain salt, fluid, and pH balance in multiple organs. In patients with cystic fibrosis, CFTR mutations cause a loss of chloride transport through CFTR that results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction and elevated sweat chloride concentrations. Most of the resulting morbidity and mortality is from pulmonary disease, which is characterised by bronchial and bronchiolar obstruction with thick tenacious secretions that are difficult to clear, colonisation by pathogenic bacteria and repeated infections. In addition, the company states there is an entire spectrum of other manifestations of cystic fibrosis that are of considerable clinical relevance, including chronic sinusitis, nasal polyps, pneumothorax, haemoptysis, cor pulmonale, impaired liver function, diabetes, pancreatitis, reduced fertility in females, and infertility in males.

Periodic increases in the severity of lung diseases, which are referred to as pulmonary exacerbations, are one of the most important clinical events in the course of the disease for people with cystic fibrosis. This is because of increased symptoms, the acceleration in the rate of decline in lung function, and the need for increased treatment. The most frequent cause of chronic pulmonary infection and exacerbations beyond infancy in people with cystic fibrosis is Pseudomonas aeruginosa, and once established, the infection is rarely completely eradicated. The presence of Pseudomonas aeruginosa in respiratory secretions is a major predictor of mortality in children with cystic fibrosis. Individuals infected with Pseudomonas aeruginosa also suffer greater morbidity with a more rapid deterioration in lung function and more rapid decline in chest radiograph score, poor growth, reduced quality of life, increased hospitalisation and increased need for antibiotic treatment. The quantity and type of Pseudomonas aeruginosa present in the lower respiratory tract changes as infection becomes established. It is known that Pseudomonas aeruginosa has two major phenotypes - mucoid and non-mucoid. Initial isolates often show a non-mucoid phenotype; however, as infection progresses a mucoid phenotype may prevail which is more difficult to eradicate with antibiotics and gives a much steeper decline in lung function. Expert opinion states that there is a significant burden of disease due to chronic infection with multi-drug resistant organisms such as non-tuberculous mycobacteria and increasingly drug resistant strains of Pseudomonas, some of which appear to be able to cause cross infection between people with cystic fibrosis.

**CLINICAL NEED and BURDEN OF DISEASE**

Cystic fibrosis has an estimated carrier rate of 1 in 25 and an incidence of 1 in 2,500 live births in the UK. Cystic fibrosis affects over 10,000 children and adults in the UK with a prevalence of 1.37 per 10,000 population. More than half of the cystic fibrosis sufferers in the UK are aged greater than 16 years. In 2014, around 31.4% of UK patients with cystic fibrosis were chronically infected with Pseudomonas aeruginosa, and 17.6% of UK patients with cystic fibrosis suffered intermittent Pseudomonas aeruginosa infections. In 2014-15, there were 13,297 admissions for cystic fibrosis (ICD-10 E84) in England, resulting in 87,618 bed days and 15,026 finished consultant episodes. In 2014 there were 111 deaths from cystic fibrosis registered in England and Wales.

b Developer provided information.
c Expert personal communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


NHS England Policies and Guidance


Other Guidance

- European Cystic Fibrosis Society. The implantation of standards of care in Europe: state of the art. 2011\(^{17}\).
- Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK. 2011\(^{18}\).
- Cystic Fibrosis Trust. Standards of care and good clinical practice for the physiotherapy management of cystic fibrosis. 2011\(^{19}\).
- Cystic Fibrosis Foundation Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: pulmonary complications: haemoptysis and pneumothorax. 2010\(^{20}\).
- Cystic Fibrosis Foundation. Evidence-based guidelines for management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. 2009\(^{21}\).
- Cystic Fibrosis Foundation Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: airway clearance therapies. 2009\(^{22}\).
- Cystic Fibrosis Trust. Antibiotic treatment for cystic fibrosis. 2009\(^{23}\).
- Cystic fibrosis pulmonary guidelines: Chronic medications for maintenance of lung health. 2007\(^{24}\).
- Cystic Fibrosis Trust. *Pseudomonas aeruginosa* infection in people with Cystic Fibrosis. Suggestions for prevention and infection control. 2004\(^{25}\).

CURRENT TREATMENT OPTIONS

As part of the comprehensive management of patients with cystic fibrosis, treatment is offered which aims to prevent infection with *Pseudomonas aeruginosa*, and to eradicate new and intermittent infections\(^{13}\). If bacterial infection is not successfully prevented or treated, a chronic infection can develop, whereby bacterial microenvironments, known as biofilms,
form\textsuperscript{13}. Treatment of airway infections are critical, so antibiotics are a key part of cystic fibrosis therapy – for prophylaxis, eradication therapy, long-term treatment of chronic infection, and treatment of acute exacerbations\textsuperscript{18}.

In people with stable disease, inhaled antibiotics have been shown to reduce concentrations of \textit{Pseudomonas aeruginosa} in sputum and to increase lung function (forced expiratory volume in one second, FEV\textsubscript{1}) two weeks after onset of treatment, suggesting their usefulness for treating exacerbations\textsuperscript{5}. Examples of nebulised antibiotics licensed for the treatment of chronic \textit{Pseudomonas aeruginosa} infection include tobramycin, colistimethate sodium and aztreonam lysine\textsuperscript{13,26}. Inhaled antibiotics can be used alone or in combination with oral antibiotics (such as ciprofloxacin)\textsuperscript{27}. Treatment with inhaled antibiotics is time-consuming for patients, with administration of nebulised antibiotics taking up to 1 hour per day during good health and longer during periods of ill health\textsuperscript{13}.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>PsAer-IgY, NCT01455675; anti-\textit{Pseudomonas} IgY vs placebo; phase III.</th>
<th>PseudIgY, NCT00633191; anti-\textit{Pseudomonas} IgY vs no treatment; phase I/II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Mukoviszidose Institut gGmbH.</td>
<td>Immunsystem AB.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{1}.</td>
<td>Trial registry\textsuperscript{28}.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK).</td>
<td>Sweden.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=164 (planned); aged 5 yrs and older; cystic fibrosis; FEV1 50-130% predicted; one or more \textit{Pseudomonas aeruginosa} positive sputum or throat cough swab or endolaryngeal suction cultures in the past 3 yrs; \textit{Pseudomonas aeruginosa} negative on study entry; no chronic \textit{Pseudomonas aeruginosa} infection; no history of allergy/hypersensitivity to hens’ egg proteins.</td>
<td>n=12 (planned); cystic fibrosis; colonised with \textit{Pseudomonas aeruginosa}; no egg allergy.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to anti-\textit{Pseudomonas} IgY 50mg gargled orally once daily; or placebo gargled orally once daily.</td>
<td>Pts received anti-\textit{Pseudomonas} IgY gargled orally once daily; or no oral IgY treatment.</td>
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<tr>
<td>Follow-up</td>
<td>Follow-up 2 yrs.</td>
<td>Not reported.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Time to the first recurrence of \textit{Pseudomonas aeruginosa} positive culture.</td>
<td>Sputum culture positive for \textit{Pseudomonas aeruginosa}.</td>
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<td>Secondary outcome/s</td>
<td>Change in FEV1; change in Body Mass Index (BMI); number of exacerbations; number of days of illness; days with antibiotic treatment; adverse effects (AEs); sputum or throat cough swab or endolaryngeal suction cultures for bacteria and fungi.</td>
<td>Pulmonary function.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as Dec 2016.</td>
<td>Study completion date reported as Dec 2018.</td>
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## ESTIMATED COST and IMPACT

### COST

The cost of anti-*Pseudomonas* IgY is not known.

### IMPACT - SPECULATIVE

#### Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability: *expert opinion states that this is a treatment that might be used to prevent infection or reduce re-infection with Pseudomonas*. *Expert opinion also notes that if effective this treatment could have a major positive impact on the health of individual patients and potentially assist with reduction of drug resistance in the cystic fibrosis population as a whole.*
- Other
- 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: *expert opinion states that they would not anticipate that this treatment would lead to an increase in burden or need for reconfiguration of service delivery unless it made a very genuine impact on mortality, such that this resulted in an older cystic fibrosis patient population.*
- None identified

#### Impact on Costs and Other Resource Use
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other: *expert opinion states that the prevalence of infection with drug resistant strains of Pseudomonas is increasing and must be a consequence of the need for aggressive antibiotic therapy to try to keep Pseudomonas infection at bay in the cystic fibrosis population. The treatment of these resistant organisms is more complex and therefore more costly than for more sensitive bugs and patients often require hospitalisation and treatment with 3 or 4 intravenous antibiotics, rather than home treatment. If this treatment is effective the quantity of nebulised antibiotics as prophylaxis and indeed intravenous antibiotic courses for*
- None identified

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*Expert personal communication.*
Exacerbations may reduce. However, there may just be a delay in chronic infection and so a shift to need this treatment in older adulthood instead and it would therefore be unlikely that this would allow any cost saving in cystic fibrosis service delivery as a whole but may have a positive impact on morbidity and mortality for people with cystic fibrosis.

Other Issues

- Clinical uncertainty or other research question identified: expert opinion notes that it is not clear from the information given as to how long this treatment may be used for but it would seem a sensible therapy to use from birth until recurrent Pseudomonas isolation indicated treatment failure.
- None identified

REFERENCES


* Expert personal communication.


