Innovation Observatory

NHS National Institute for Health Research

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Cysteamine bitartrate for cystic fibrosis exacerbations

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Developer/Company	NovaBiotics Ltd	**UKPS ID**	N/A

SUMMARY

Oral cysteamine bitartrate (capsule) is in clinical development to treat pulmonary exacerbations in people with cystic fibrosis (CF). CF is a life-limiting, inherited disease caused by a defective gene which results in lungs, the digestive system, and other tissues becoming congested with thick mucus. The presence of the mucus in the airways of CF patients leads to numerous health issues, including chronic and recurrent infections of the lungs and consequent inflammation, reduction of lung function, and breathing difficulties. Some patients with CF may be symptom-free when well, but many will have chest symptoms such as cough and sputum production.

Cysteamine bitartrate as an oral formulation is a novel treatment of exacerbations of CF-associated lung disease, with a unique multi-action: breaking down of the excessive mucus produced by the lining of the airways, killing of the bacteria responsible for the recurrent respiratory infections, and disrupting the biofilms in which they colonise. Cysteamine bitartrate also potentiates the activity of standard of care antibiotics used in CF patients, and is potentially antibiotic-sparing as an adjunct treatment alongside standard of care therapy. If licensed, cysteamine bitartrate will offer an additional treatment option for adult patients with CF exacerbations.

PROPOSED INDICATION

Treatment of cystic fibrosis (CF) exacerbations in adults.[a]

TECHNOLOGY

DESCRIPTION

Cysteamine bitartrate (Lynovex; NM001) as an oral formulation is in clinical development for CF exacerbations.[1] Cysteamine bitartrate is an endogenous product of coenzyme A metabolism via the action of the vanin pantetheinase ectoenzymes.[2,3] Cysteamine bitartrate is weakly antimicrobial in vitro when used alone, inhibits biofilm formation, and is potently mucoactive.[2, 4] Cysteamine bitartrate has broad spectrum antibiotic potentiating activity against a wide range of pathogens including (but not limited to) those which are associated with lung function decline in CF.[5]

The phase IIb clinical trial (CARE-CF1, NCT03000348) assessed the effects of two weeks of oral (capsule) cysteamine bitartrate treatment as an adjunct to standard of care therapy (SOCT) in CF, compared to placebo plus SOCT.[a,6]

Patients in the active comparator arms of the trial received one of the following dosing regimens: [7]

- One oral dose of cysteamine bitartrate (high dose) per day, in the morning. The patient takes two oral placebo doses, one at mid-day and one in the evening.
- Two oral doses of cysteamine bitartrate (high dose) per day, one in the morning and one in the evening. The patient takes one oral placebo dose, at mid-day.
- Three oral doses of cysteamine bitartrate (high dose) per day, one in the morning, one at mid-day and one in the evening.
- Three oral doses of cysteamine bitartrate (low dose) per day, one in the morning, one at mid-day and one in the evening.
- Three oral doses of cysteamine bitartrate (mid-range dose) per day, one in the morning, one at mid-day and one in the evening.

Treatment duration and dosing specifics are not stated on the trial registry.[7]

The company anticipate commencing a pivotal phase III clinical trial in 2019.[a]

INNOVATION AND/OR ADVANTAGES

As a first-in-class combination mucolytic-antibiofilm-antimicrobial agent, cysteamine bitartrate in oral form has the potential to offer a novel way forward in the treatment of the chronic and recurrent respiratory infections that are linked to pulmonary exacerbations of CF.

Cysteamine bitartrate is active against emerging, very difficult to treat CF bacteria with significant negative prognostic impact.[2,4] Cysteamine bitartrate breaks down the thick, sticky mucus produced by the lining of the airways in CF patients, and kills the bacteria that thrive in this environment and occasionally "flare" as serious chest infections (exacerbations).[8]

CF patients are exposed to a range of antibiotics to control bacteria during stable periods of disease and specific antibiotic interventions during exacerbations which are driven by bacteria that flare

[a] Information provided by company

despite long term antibiotic therapy.[4] However, studies have shown that a proportion of CF patients develop resistance to antibiotics used for the treatment of exacerbations.[9,10]

Cysteamine bitartrate could potentially break the cycle of progressive lung damage and recurrent infections in CF, with the manifold actions of mucus and biofilm disruption and antimicrobial impact on the bacteria these structures support achieving this end. As an adjunct treatment, cysteamine bitartrate may extend the utility and lifespan of conventional antibiotics, whilst at the same time potentially reducing dosing levels and frequency.[4]

Cysteamine bitartrate can also be used alongside the more recently approved 'disease modifiers' that can work in certain patients to correct or potentiate the faulty cystic fibrosis transmembrane conductance regulator (CFTR) protein that causes the disease. Cysteamine bitartrate oral is a therapy designed to treat all CF patients and is not specific to patients with specific mutations/disease genotypes.[8]

The oral presentation of cysteamine bitartrate is advantageous as the very poor ventilatory function of exacerbating CF patients does not facilitate optimal exposure to inhaled products.[b] The novel mucolytic-antimicrobial activity of cysteamine bitartrate provides potential for a much needed new therapeutic strategy in CF, as exacerbation specific interventions are limited.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Cysteamine bitartrate is already established in clinical practice for an unrelated orphan condition, cystinosis, and is therefore being repurposed in a new oral form for CF.[4]

- Cysteamine bitartrate is a designated orphan drug in the EU and USA in 2011 and 2014, respectively, for CF[11,12]
- Cysteamine bitartrate was awarded Fast Track designation for CF exacerbations by the FDA in March 2018[8]

PATIENT GROUP

DISEASE BACKGROUND

CF is an autosomal recessive, progressive, and usually fatal genetic disease. CF is most common in the Caucasian population, and is considered an orphan disease.[20] Lack of properly functioning CFTR ion channel is responsible for the clinical sequelae of CF. This includes malabsorption of nutrients and the inability to mobilise tenacious respiratory secretions, leading to recurrent pneumonia and lung damage. There are over 2,000 mutations in the CFTR gene, some of which, when present in one or both CFTR alleles, result in the clinical constellation that is CF.[13]

Symptoms of CF tend to start in early childhood, although they can sometimes develop very soon after birth, or may not be obvious until adulthood. Some of the main symptoms of CF can include:

- recurring chest infections
- difficulty putting on weight
- frequent, wet-sound coughs
- diarrhoea
- occasional wheezing and shortness of breath

People with CF can also develop a number of related conditions, including diabetes (up to 40-50% in adults), osteoporosis (23%), liver problems (gallbladder abnormalities occur in 24–50%, hepatic steatosis 23–75%), sinus disease (up to 65%) and fertility problems (male infertility occurs in 98%).[14,15,16]

Exacerbations, intermittent episodes of acute worsening of CF symptoms often as a result of bacterial infection, are a key feature of cystic fibrosis. They are the principle cause of morbidity and mortality as a result of the decline in lung function. A typical adult patient would have multiple exacerbations annually.[1] With the current SOCT, a large proportion of CF patients do not recover their lung function to the pre-exacerbation level, and lung function declines over the course of their lifetime.[17,18]

Pulmonary exacerbations can have a negative impact on health-related quality of life that lasts long after the pulmonary exacerbation has resolved.[19] CF is a progressive condition, worsening over time and eventually the condition can be fatal if it leads to a serious infection or the lungs cease to work properly.[15]

CLINICAL NEED AND BURDEN OF DISEASE

The incidence of CF varies between populations: the condition is considerably less common in Asian and African populations than in the white populations of Europe and North America, with variations within each country. The exact prevalence in Europe is unknown, but estimates range between 1 in 8,000 and 1 in 10,000 individuals.[20]

In the UK, CF is estimated to occur in around 1 in 2,500 live births with approximately 200 to 300 new diagnosis annually.[21] The latest UK Cystic Fibrosis Registry indicates a total of 10,461 people living with CF in the UK in 2016, of which 247 were newly diagnosed.[22]

Median survival ages for people with one or two copies of F508del, diagnosed at birth, were 46 years for males and 41 for females. This represents around 95% of the UK CF population. For those with two copies of F508del (approximately 40-50% of that group), the median survival age for those who live to age 30 rises to 52 for men and 40 for females.[23]

The 2016/17 Hospital Episodes Statistics for England recorded 16,287 finished consultant episodes (FCE), 13,879 admissions and 5,435 days cases for cystic fibrosis (ICD-10 code: E84).[24]

Treatment of exacerbation requires healthcare resource utilisation including hospitalisation, emergency room use (3% of all hospital treated exacerbations), and specialist (pulmonologist) visits (2% of all hospital treated exacerbations), as well was routine outpatient visits. In the UK, over half (57%) of patients had at least one pulmonary exacerbation requiring hospitalisation per year. Of those, 50% required home IV antibiotics after discharge and 95% required oral antibiotics.[19]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

CF is the most common life-limiting autosomal recessively inherited condition in the UK. It is a multisystem disorder but lung disease is the major cause of significant morbidity and mortality.[25]

CF can be diagnosed based on: [26]

- positive test results in people with no symptoms, for example infant screening (blood spot immunoreactive trypsin test) followed by sweat and gene tests for confirmation
- clinical manifestations, supported by sweat or gene test results for confirmation
- clinical manifestations alone, in the rare case of people with symptoms who have normal sweat or gene test results

Care for people with CF should be provided by a specialist CF multidisciplinary team based at a specialist CF centre. The aim of CF care is to prevent or limit symptoms and complications of the condition, and routine monitoring and annual assessments are crucial in providing effective care.[26]

Current treatments for CF generally manage the complications rather than the cause of the disease. Treatments can be broadly classified as: nutritional repletion (for example, pancreatic enzymes and nutritional supplements); relief of airway obstruction (for example, physiotherapy, drugs to improve clearance of mucus such as dornase alfa [rhDNase], hypertonic saline, and bronchodilators); treatment of acute infections; suppression of chronic infection; suppression of inflammation (for example, steroids, high dose ibuprofen) and lung transplantation.[27]

People with CF and their family members or carers will need emotional support and some may need specialist psychological support at diagnosis, during times of transition, in relation to fertility, to cope with complications, when waiting for or having organ transplantation, and when approaching the end of life.[26]

CURRENT TREATMENT OPTIONS

Pulmonary management in CF may include:[25,26,28]

Immunomodulatory agents

- For people with CF and deteriorating lung function or repeated pulmonary exacerbations offer long-term treatment with azithromycin at an immunomodulatory dose. For people who have continued deterioration in lung function, or continuing pulmonary exacerbations while receiving long-term treatment with azithromycin, stop azithromycin and consider oral corticosteroids. Do not offer inhaled corticosteroids as an immunomodulatory treatment for people with CF.

Mucoactive agents

- Offer a mucoactive agent to people with CF who have clinical evidence of lung disease. Offer rhDNase (dornase alfa; recombinant human deoxyribonuclease) as the first choice of mucoactive agent. If clinical evaluation or lung function testing indicates an inadequate response to rhDNase, consider both rhDNase1 and hypertonic sodium chloride or hypertonic sodium chloride alone.
- Mannitol dry powder for inhalation is recommended as an option for treating CF in adults who: cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and whose lung function is rapidly declining (forced expiratory volume in 1 second (FEV1) decline greater than 2% annually) and for whom other osmotic agents are not considered appropriate. People currently receiving mannitol whose CF does not meet this criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.
- Lumacaftor–ivacaftor is not recommended by NICE, within its marketing authorisation, for treating cystic fibrosis in people 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

Treating pulmonary infection

- Pulmonary infections may include aspergillus fumigatus complex, burkholderia cepacia complex, haemophilus influenza, non-tuberculous mycobacteria, pseudomonas aeruginosa, staphylococcus aureus, and unidentified infections. Antibiotics should be targeted against common CF bacteria and these can be given orally, although intravenous antibiotics will be required for ongoing symptoms or severe exacerbations.

Treating acute respiratory exacerbation

- Acute pulmonary exacerbations are treated with a combination of oral or/and IV antibiotics depending on the severity of the illness

PLACE OF TECHNOLOGY

If licensed for CF exacerbations, adjunct to SOCT, cysteamine bitartrate will offer an additional treatment option for patients who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	CARE-CF1, NCT03000348, EudraCT2015-004986-99, NBTCS02; cysteamine bitartrate vs placebo; phase IIb
Sponsor	NovaBiotics Ltd
Status	Complete but unpublished
Source of Information	Trial registry[7,29], manufacturer[6]
Location	EU (incl UK) and USA
Design	Randomised, double-blind, placebo-controlled
Participants	n=91; ≥18 years of age; CF-associated lung disease with documented history of chronic infection with Gram-negative organism(s); established patient of the Principal Investigator's CF Multi Disciplinary Team (MDT); weight >40 kg; FEV1 >30% of predicted within the 6 months prior to study exacerbation; experiencing a new exacerbation of CF-associated lung disease (based on Investigator assessment of ≥4 symptoms present on the Fuchs' criteria) at baseline visit requiring treatment that includes an aminoglycoside antibiotic
Schedule	The study has 6 arms. Patients are randomised to one of the following arms: 1. **High dose, once per day** - one oral dose of cysteamine (high dose) per day, in the morning. The patient takes two oral placebo doses, one at mid-day and one in the evening. 2. **High dose, twice per day** - two oral doses of cysteamine (high dose) per day, one in the morning and one in the evening. The patient takes one oral placebo dose, at mid-day. 3. **High dose, three times per day** - three oral doses of cysteamine (high dose) per day, one in the morning, one at mid-day and one in the evening. 4. **Low dose, three times per day** - three oral doses of Cysteamine (low dose) per day, one in the morning, one at mid-day and one in the evening. 5. **Mid-range dose, three times per day** - three oral doses of cysteamine (mid-range dose) per day, one in the morning, one at mid-day and one in the evening. 6. **Placebo** – three oral doses of placebo, one in the morning, one at mid-day and one in the evening. Treatment duration was comprised of two weeks of cysteamine bitartrate treatment as an adjunct to SOCT in CF, compared to placebo plus SOCT. Dosing specifics are not stated on the trial registry.
Follow-up	Follow-up was not reported on the trial registry.
Primary Outcomes	• Change from baseline in sputum bacterial load [Time frame: Baseline through Day 21/end of study] • Safety and tolerability assessed by the number of subjects with Adverse Events [Time frame: Baseline through Day 21/end of study]

Secondary Outcomes	• Change from baseline in neutrophil elastase levels [Time frame: Baseline through Day 21/end of study] • Change from baseline in sputum IL8 [Time frame: Baseline through Day 21/end of study] • Change from baseline in FEV1 [Time frame: Baseline through Day 21/end of study] • Change from baseline in Weight and BMI [Time frame: Baseline through Day 21/end of study] • Change from baseline in C-Reactive Protein [Time frame: Baseline through Day 21/end of study] • Change from baseline in blood leukocyte count [Time frame: Baseline through Day 21/end of study] • Assessment of blood cysteamine levels [Time frame: Day 14] • Assessment of sputum cysteamine levels [Time frame: Day 14] • Change from baseline in CFRSD-CRISS [Time frame: Baseline through Day 21/end of study] • Change from baseline in CFQ-R [Time frame: Baseline through Day 21/end of study] • Change from baseline in Jarad and Sequeiros Symptom Score Questionnaire [Time frame: Baseline through Day 21/end of study] • Patient Global Assessment of Exacerbation outcome [Time frame: Day 14]
Key Results	No drug related SAEs were reported, in keeping with the safety and tolerability previously reported for cysteamine bitartrate in CF patients in an earlier phase IIa study. The initial efficacy outcomes measured in CARE CF 1 were the reduction in the number of bacteria in sputum, improvement in patient reported outcome scores of CF respiratory symptom severity and improvement in lung function (FEV1) following two weeks of treatment. A statistically and clinically significant, dose and regimen specific reduction in CF respiratory symptom severity was identified in patients taking cysteamine bitartrate plus SOCT versus those on placebo plus SOCT after two weeks of treatment. The same dosing regime also resulted in a clinical and statistically significant reduction in blood white cell count after two weeks when compared with placebo. These cysteamine bitartrate specific improvements were mirrored by changes in health-related questionnaire scores, sputum levels of inflammatory mediators and a 4% increase in lung function (change in % predicted FEV1 > placebo response) after two weeks of treatment. The sputum of patients taking cysteamine bitartrate also contained less bacteria (per ml of sputum) than sputum from patients who received only placebo plus their SOCT antibiotic treatment.
Adverse effects (AEs)	No drug related severe AEs were reported.
Expected reporting date	Actual primary and study completion date reported as April 2018.

ESTIMATED COST

The cost of oral cysteamine bitartrate for CF exacerbations is not yet known.

Cysteamine as mercaptamine bitartrate (Cystagon) is already marketed in the UK for the treatment of proven nephropathic cystinosis; 100 x 50mg capsules costs £70, and 100 x 150mg capsules costs £190 (NHS indicative price).[30,31]

ADDITIONAL INFORMATION

NovaBiotics Ltd

NovaBiotics Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation [ID1303]. Suspended in Aug 2018.
- NICE technology appraisal guidance. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation (TA398). July 2016.
- NICE technology appraisal guidance. Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (TA276). March 2013.
- NICE technology appraisal guidance. Mannitol dry powder for inhalation for treating cystic fibrosis (TA266). November 2012.
- NICE clinical guideline. Cystic fibrosis: diagnosis and management (NG78). October 2017.
- NICE quality standard. Cystic fibrosis (QS168). May 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Respiratory Services: Cystic Fibrosis Adults. A01/S/a.

OTHER GUIDANCE

- European Cystic Fibrosis Society (ECFS). ECFS best practice guidelines: the 2018 revision. 2018[32]

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