National Institute for Health Research

NIHR Innovation Observatory
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Cysteamine bitartrate (Procysbi) – delayed release for Huntington's Disease

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LAY SUMMARY

Huntington's disease (HD) is an inherited progressive brain disorder, which destroys brain cells. It usually appears in a person's thirties or forties with early symptoms of the disease including irritability, depression, small involuntary movements, poor coordination, and trouble learning new information. Once these symptoms started, patients are expected to live 15 to 20 more years.

There is no cure for the disease and currently its progress cannot be reversed or slowed down. However, some of the symptoms of the disease can be managed with medication and therapies.

If licensed, cysteamine bitartrate will offer a viable treatment option for patients with Huntington's disease which may stall neural degeneration and clinical decline; slowing the progression of the disease.

TARGET GROUP

- Adults with Huntington's disease

TECHNOLOGY

DESCRIPTION

Cysteamine Bitartrate (delayed release) [cysteamine bitartrate (delayed release) (capsule); cysteamine bitartrate (delayed release) (tablet); cysteamine bitartrate, Bennu; cysteamine bitartrate, Bennu (capsule); cysteamine bitartrate, Bennu (tablet); DR cysteamine; DR Cysteamine (capsule); DR Cysteamine (tablet); EC cysteamine; EC Cysteamine (capsule); EC Cysteamine (tablet); Procysbi; Procysbi (capsule); Procysbi (tablet); RP-103; RP-103 (capsule); RP-103 (tablet); RP-104 (tablet); RP103; RP103 (capsule); RP103 (tablet); RP104 (tablet)Procysbi; RP-103; Mercaptamine bitartrate delayed-release] is an enterically-coated, delayed-release formulation of cysteamine bitartrate contained in a gelatin capsule, developed by Horizon Pharma (formerly Raptor Pharmaceutical) for the treatment of pancreatic cancer, nephropathic cystinosis and neurodegenerative diseases. It is also under development for the treatment of Leigh syndrome and other mitochondrial disorders. It was previously under development for steatohepatitis (NASH).

Cysteamine bitartrate is expected to work by blocking the activity of certain enzymes which are believed to be involved in the development of nerve damage in Huntington's disease patients. Blocking the action of these enzymes is expected to improve the motor function of patients and to improve survival times.

In the phase II/III clinical trial, 16 cysteamine bitartrate capsules are taken per day for 18 months.

Cysteamine bitartrate has an orphan drug status granted for Huntington's disease, as well as for the treatment of pancreatic cancer, cystinosis and nephropathic cystinosis.

Cysteamine bitartrate is already licensed in the EU for nephropathic cystinosis.[1]

INNOVATION and/or ADVANTAGES

If licensed, cysteamine bitartrate will offer a viable treatment option for patients with Huntington's disease and may slow down the progression of the disease. At present, the standard of care for HD is limited to therapies that can help to minimize some of the symptoms, however, do not slow disease progression by targeting the underlying cause of the disease.[2]

DEVELOPER

Raptor Pharmaceuticals

AVAILABILITY, LAUNCH or MARKETING

Cysteamine bitartrate for Huntington's disease is currently in clinical trials phase 3.

PATIENT GROUP

BACKGROUND

Huntington's disease is a progressive brain disorder. It usually appears in a person's thirties or forties and causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). Irritability, depression, small involuntary movements, poor coordination, and trouble learning new information count to early signs and symptoms. Jerking or twitching movements, known as chorea, pronounce as the disease progresses. Changes in personality, trouble walking, speaking, and swallowing occur. Once the symptoms commence individuals are expected to live 15 to 20 more years.[3]

Huntington's disease is caused by genetic changes, mutations in the huntingtin gene (HTT), which provides instructions for making a protein called huntingtin. The function of this protein is unknown, however, it appears to play an important role in nerve cells (neurons) in the brain. HTT involves a DNA segment know as CAG trinucleotide repeat. It is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Whereas the segment is usually repeated 10 to 35 times within a row, in people with Huntington's disease, the CAG segment is repeated 36 to 120 times. This leads to dysfunction and eventual death of neurons in certain areas of the brain.[3]

CLINICAL NEED and BURDEN OF DISEASE

The prevalence of Huntington's disease in the UK is uncertain, however, it has been suggested that it may be greater than previously reported. A study shows that the estimated prevalence of over 21 year olds rose from 5.4 in 1990 to 12.3 in 2010 (expressed per 100 000 population). The most dramatic increased prevalence was seen in 51 to 60 year olds.[4]

There is still no cure for Huntington's disease, which makes research into the condition enormously important. A fault on chromosome 4 is passed down through families. In case one parent is affected with the disease, a 50/50 chance of inheriting the gene exists.[5]

Pneumonia, followed by cardiovascular diseases, are the most common causes of death in patients with HD.[6]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Dementia: Supporting people with dementia and their carers in health and social care [CG42]. November 2006.

NHS ENGLAND and POLICY GUIDANCE

No guidance is currently available.

OTHER GUIDANCE

No guidance is currently available.

CURRENT TREATMENT OPTIONS

There is no cure for Huntington's disease and currently its progress cannot be reversed or slowed down. However, some of the features of the disease can be managed with medication and therapies, such as speech and language therapy or occupational therapy. These help patients with their communication and day-to-day living. Medication in most of the cases has side effects.[7]

Antidepressants to treat depressions that arise with the disease are often used to help improve mood swings, e.g. SSRI such as fluoxetine, citalopram, paroxetine; tricyclic antidepressants such as amitriptyline and other types such as mirtazapine, duloxetine or venlafaxine. Furthermore, side effects include constipation, sweating, shaking or insomnia. Mood stabilisers, particularly carbamazepine, are used to treat irritability or mood swings. Medication to suppress involuntary movements, such as antipsychotic medication (olanzapine, sulpiride, risperidone, quetiapine), tetrabenazine, and benzodiazepines (clonazepam, diazepam) are widely used. Stiffness, rigidity, sedation, tremor or slow movements can occur as side effects.[7]

EFFICACY and SAFETY

Trial	CYST-HD EudraCT Number: 2010-019444-39 NCT02101957 PHRC2004-03bis TrialTroveID-100381
Sponsor	(Other government agency), (Other Hospital/Academic/Medical Center)
Status	Completed.
Source of Information	Trialtrove.
Location	France.
Design	Randomized, efficacy, safety, placebo control, double blinded, open label, multiple arm
Participants	N=96. 18 to 65 years. Patients with Huntington's Disease. Clinically registered for at least one year illness, which led to consult (abnormal movements, neuropsychiatric disorders, neuropsychological impairment). UHDRS motor > = 5 Patient self TFC >10(>=11) Huntington's disease demonstrated by the presence of an abnormal number of trinucleotide: CAG>38 in the first exon of the huntingtin gene.
Schedule	This 36-month randomized trial is comprised of an 18-month blinded, placebo-controlled phase followed by an 18-month open label phase in which all patients transition to RP103. Patients to be treated with delayed-release cysteamine bitartrate or placebo. In open-label extension phase, all patients on the placebo capsules rolling onto DR Cysteamine and all other patients continuing on DR Cysteamine for up to an additional 18 months. Patients were allowed to continue their baseline medication regime, including antidepressants and tetrabenazine. Patients were not randomized in the study based on concomitant medications. Patients were treated in 1:1 ratio. Number of Arms: 2. Arm 1: Experimental: RP103 RP103 Capsule, 16 capsules per day Assigned Interventions: Drug RP103 Arm 2: Placebo Comparator: placebo capsule, 16 capsules per day Assigned Interventions: Drug: Placebo
Follow-up	Not reported.

Primary Outcomes	Safety and potential efficacy of delayed-release cysteamine bitartrate in patients with Huntington's Disease. Potential mechanism in HD patients, using BDNF as a biomarker of potential efficacy. Effect of cysteamine in patients with symptomatic HD by comparing two groups of patients on the results of the Unified HD Rating Scale.
Secondary Outcomes	To measure brain-derived neurotrophic factor (BDNF) levels. Confirm this activity by comparing the two groups with functional, neuropsychological and psychiatric scales. To evaluate function included the UHDRS-TFC and Independence Scale.
Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	Not reported.

ESTIMATED COST and IMPACT

COST

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

- ☒ Reduced mortality/increased length of survival
- ☒ Reduced symptoms or disability
- ☒ Other: improved patient convenience, wider societal benefits
- ☐ 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
- ☒ 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
- ☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

1 [cited; Available from: http://ir.raptorpharma.com/releasedetail.cfm?ReleaseID=863840

2 Raptor Pharmaceuticals. Completes Enrollment in Phase 2/3 Clinical Trial of RP103 for the Potential Treatment of Huntington's Disease. Novato, California 2012.

3 Genetics Home Reference. Huntington Disease. 2017:7030 Cysteamine bitartate

4 Evans SD, I; Rawlins, MD; Wexler, NS; Tabrizi, SJ; Smeeth, L;. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. Journal of neurology, neurosurgery, and psychiatry. 2013;84(10):1156-60.

5 Brain Research Trust. Huntington's Disease. [cited 2017 27.03.]; Available from: http://www.brt.org.uk/huntingtons-disease?gclid=CJeC6rW-9tICFZQy0wodwMILCQ

6 Heemskerk A RR. Aspiration pneumonia and death in Huntington's disease. PLOS Currents Huntington Disease,. 2012;1.

7 NHS Choices. Huntington's Disease - Symptoms. 2014 [cited 2017 27.03.]; Available from: http://www.nhs.uk/Conditions/Huntingtons-disease/Pages/Symptoms.aspx