Cerliponase alfa for neuronal ceroid lipofuscinosis type 2 (CLN2 disease)

LAY SUMMARY

Neuronal ceroid lipofuscinosis (or CLN2 disease) is a very rare inherited disease that affects young children. The disease affects brain cells, and leads to blindness, fits (epilepsy), difficulties with movements and learning difficulties. At the moment, there is no cure, and even with current treatments, children usually die by the age of 12 years old.

Cerliponase alfa is a new drug being developed to treat neuronal ceroid lipofuscinosis. It has to be given in hospital every two weeks. A study is currently looking to see whether cerliponase alfa helps to slow down the disease and is safe for to take. If it is licensed for use in the UK, cerliponase alfa will be the first drug available to treat this rare childhood disease.

NIHR HSRIC ID: 9876
TARGET GROUP

- Neuronal ceroid lipofuscinosis type 2 (CLN2).

TECHNOLOGY

DESCRIPTION

Cerliponase alfa (BMN-190) is a recombinant form of human tripeptidyl peptidase-1 (TPP1), the lysosomal enzyme deficient in patients with neuronal ceroid lipofuscinosis type 2 (also termed CLN2 disease). A deficiency of TPP1 results in abnormal storage of proteins and lipids in neurons and other cells causing impaired cellular function. Cerliponase alfa is an enzyme replacement therapy designed to restore TPP1 enzyme activity and break down the lysosomal storage materials that cause the signs and symptoms of CLN2. In clinical trials, cerliponase alfa is administered by intracerebroventricular (ICV) infusion, with participants receiving cerliponase alfa 30-300mg every other week for 48 weeks.

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

INNOVATION and/or ADVANTAGES

If licensed, cerliponase alfa will offer a treatment option for patients with CLN2 disease, who currently have no disease modifying or curative therapies available.

DEVELOPER

BioMarin Pharmaceutical.

AVAILABILITY, LAUNCH OR MARKETING

Phase II clinical trials.

PATIENT GROUP

BACKGROUND

CLN2 is a rare genetic disease caused by the deficiency of an enzyme called TPP1. CLN2 is one form of neuronal ceroid lipofuscinosis (NCL), also known as Battens disease. NCLs are a group of inherited progressive degenerative brain diseases characterised clinically by a decline of mental and other capacities, epilepsy, and vision loss through retinal degeneration, and histopathologically by intracellular accumulation of an auto-fluorescent material, ceroid lipofuscin, in the neuronal cells in the brain and retina. The exact prevalence and incidence of this group of disorders are unknown.

Deficiency of TPP1 is caused by mutations in the CLN2 gene and is inherited in an autosomal recessive fashion.

The onset of CLN2 is slowly progressive. Children are healthy and develop normally for the first few years of life, but the disease then progresses with rapid deterioration. The first
symptoms often begin with increasing visual impairment resulting in blindness, complex epilepsy with severe seizures that are difficult to control, myoclonic (rapid involuntary muscle spasm) jerks of limbs, difficulties sleeping, the decline of speech, language and swallowing skills, and a deterioration of fine and gross motor skills that result in the loss of mobility. Ultimately the child or young person will become totally dependent on families and carers for all of their needs. Other symptoms that are commonly experienced include hallucinations, memory loss and challenging behaviours. Death is inevitable and usually occurs between the ages of 6 and 12 years.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:
- Clinical Commissioning Policy: Pre-implantation Genetic Diagnosis (PGD). E01/P/a.

**CLINICAL NEED and BURDEN OF DISEASE**

The population likely to be eligible to receive cerliponase alfa could not easily be estimated from available routine published sources. In 2013-14, there were 49 admissions for NCLs in England, resulting in 218 bed days and 56 finished consultant episodes. An epidemiological study into neurological deterioration in childhood identified 141 cases of NCL (all forms) in the UK over a 12 year period.

The Batten Disease Family Association estimates that about 1-3 children are diagnosed with an infantile form of Battens disease and approximately 7-10 children are diagnosed with the late-infantile form each year in the UK. This equates to about 15-30 children and 30-60 children affected by early and late onset NCLs in the UK, respectively. A minority of patients with the late infantile form of Batten disease may not have CLN2 disease, and conversely not all patients with CLN2 disease have the late infantile form. With these factors considered, as well as the given life expectancy range, the company estimate there are approximately 19 to 38 patients in the UK living with the CLN2 associated form of NCL.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
- No relevant guidance identified.

**Other Guidance**
- No relevant guidance identified.

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* Company provided information.
CURRENT TREATMENT OPTIONS

There is currently no curative treatment for CLN2. Treatment options are currently symptomatic and palliative only, aiming to delay onset and improve quality of life. Seizures, malnutrition, gastroesophageal reflux, pneumonia, depression, anxiety, spasticity, Parkinsonian symptoms, and dystonia can be effectively managed through medication and physical therapy. Prevention, monitoring and managing of complications (due to immobility and loss of function) is also recommended (for example, management of malnutrition, gastroesophageal reflux and aspiration pneumonia).

Children often receive polypharmacotherapy and clinicians need to balance symptom control with the adverse effects of multiple medications. Early in the disease, therapies are administered in an attempt to prolong function, but treatment goals soon evolve to supporting quality of life once all function is lost.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01907087, EudraCT2014-003480-37, 190-202; cerliponase alfa; phase I/II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>BioMarin Pharmaceutical.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK) and USA.</td>
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<tr>
<td>Design</td>
<td>Uncontrolled, open-label.</td>
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<tr>
<td>Participants</td>
<td>n=24 (planned); aged 3-6 years; diagnosis of CLN2 determined by TPP1 enzyme activity (dried blood spot); mild to moderate disease documented by a two-domain score of 3-6 on motor and language domains of the Hamburg Scale, with a score of at least 1 in each of these two domains; seizures must be stable.</td>
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<tr>
<td>Schedule</td>
<td>Participants receive cerliponase alfa 30-300mg via ICV infusion administered every other week for at least 48 weeks. First 6 subjects participated in a dose escalation phase of between 30-300mg up to a stable dosage of 300mg, the remaining subjects received 300mg doses.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment for 48 weeks.</td>
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<tr>
<td>Primary outcome</td>
<td>Safety and efficacy according to changes in clinical measures as determined by the CLN2 disease rating scale.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Changes in clinical measures as determined by magnetic resonance imaging (MRI) and pharmacokinetics. Exploratory outcomes include changes from baseline in CLN2 disease specific quality of life score and Denver II development score.</td>
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<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as March 2016.</td>
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ESTIMATED COST and IMPACT

COST

The cost of cerliponase alfa is not yet known.

\textsuperscript{b} Company provided information.
IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Reduced symptoms or disability: disability reduced but will not be eliminated, therefore children likely to continue to have significant health needs, but possibly with increased life expectancy.
- Other
- No impact identified

Impact on Health and Social Care Services

- Increased use of existing services
- Re-organisation of existing services
- Other: this treatment schedule is intensive with hospitalisations every 2 weeks. It is highly demanding on patients, families, carers and hospital/community resources.
- Decreased use of existing services
- Need for new services
- None identified

Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Other increase in costs
- None identified

Other Issues

- Clinical uncertainty or other research question identified: expert opinion notes that there is still clinical uncertainty pending publication of efficacy and safety data. A long-term follow up will be needed. Investigation into family decision making and burden of care with/without this treatment will be necessary if the treatment is approved.
- None identified

REFERENCES


* Expert personal communication.