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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Tofersen for the treatment of amyotrophic lateral sclerosis caused by mutations in the SOD1 gene

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Developer/Company	Biogen	**UKPS ID**	651777

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Tofersen (BIIB067) is in clinical development for the treatment of amyotrophic lateral sclerosis (ALS – also known as motor neurone disease) caused by mutations in the SOD1 gene (SOD1-ALS). ALS is a progressive disease of the nervous system, where nerve cells in the brain and spinal cord that control voluntary movement gradually deteriorate, causing loss of muscle function and paralysis. ALS is a debilitating and life-threatening disease. The gradual loss of neurons leads to a paralysing effect on muscles used for breathing, which usually leads to death from respiratory failure.

Tofersen is designed to help some patients with ALS who have a change in the gene responsible for producing the enzyme SOD1. Mutations in the SOD1 gene confer a new toxic property to the SOD1 protein, though exactly how disease-associated SOD1 is toxic to neurons is unknown. Tofersen is made of a small strand of synthetic genetic material that prevents translation of SOD1. By reducing the amount of both normal and defective SOD1, tofersen is expected to improve the progression of SOD1-ALS. Tofersen is given as an intrathecal injection and if licensed, it will offer a treatment option for patients with SOD1-ALS who currently have very limited available options.

PROPOSED INDICATION

Treatment of amyotrophic lateral sclerosis (ALS) caused by mutations in the SOD1 gene (SOD1-ALS).[1,2]

TECHNOLOGY

DESCRIPTION

Tofersen (BIIB067) is an antisense oligonucleotide (ASO) being developed for adults with ALS caused by mutations in the gene that encodes the superoxide dismutase 1 (SOD1) protein.[3-5] SOD1 is an enzyme that neutralizes harmful radical oxygen molecules. Mutations in SOD1 can cause the enzyme to misfold as it is being made, which may lead to a toxic build-up of misfolded protein.[6] Tofersen binds to the SOD1 mRNA, leading to the destruction of the mRNA, thus reducing the levels of SOD1 protein production. This is hypothesised to decrease the toxicity associated with the mutant SOD1 gene and may therefore slow clinical progression and prolong survival.[7]

Tofersen is in phase III clinical development for the treatment of ALS caused by mutations in the SOD1 gene.[1,2] Tofersen dosing is 100 mg administered as an intrathecal injection with three loading doses administered every two weeks and then four-weekly interval dosing thereafter.[a]

INNOVATION AND/OR ADVANTAGES

Treatment options for patients with ALS are extremely limited with no drugs currently available that significantly slow progression.[8] Riluzole (Rilutek) is currently the only drug licensed for treating ALS in the UK. The licensed indication of riluzole is to extend life or the time to mechanical ventilation for individuals with ALS.[9]

As tofersen is an ASO targeting the genetic driver of the disease, it may be able to provide therapeutic benefit through improved survival and function to people with ALS with SOD1 mutations.[10]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tofersen does not currently have a Marketing Authorisation in the EU/UK for any indication.

Tofersen was designated as an orphan drug in the EU in August 2016 for the treatment of ALS.[11]

[a] Information provided by Biogen.

PATIENT GROUP

DISEASE BACKGROUND

Motor neurone disease (MND) describes a group of diseases that affect the nerves (motor neurones) in the cerebral cortex and spinal cord that tell the muscles what to do.[12] With MND, the death of these large motor neurones in the cerebral cortex and spinal cord causes progressive muscle weakness, atrophy and, ultimately, paralysis and death within 3 to 5 years after disease onset.[13,14]

MND can affect how a person walks, talks, eats, drinks and breathes. MND causes a range of symptoms, which progress at varying speeds.[12] Early symptoms can include: weakness in your ankle or leg, slurred speech, a weak grip, muscle cramps and twitches, weight loss, difficultly stopping crying or laughing in inappropriate situations and impacts psychological health.[15,16]

The order of appearance of symptoms varies between individuals.[12] There are five main types of MND.[17] ALS is the most common form of MND, with weakness and wasting in the limbs, muscle stiffness and cramps. Over time, as ALS progresses, different areas of the body become involved. Involvement of the muscles controlling speech, swallowing and breathing can also occur.[12]

Most cases of ALS are sporadic (sALS), while approximately 5–10% cases are familial ALS (fALS).[18] Thus far, ALS-causing mutations have been identified in more than 25 genes, including SOD1.[18,19] Mutations in SOD1 are one of the most common and important causes of fALS.[20] More than 185 mutations in SOD1 have been reported to date.[21]

CLINICAL NEED AND BURDEN OF DISEASE

A systematic review of global epidemiology of ALS reports a European median (IQR) incidence rate (/100,000 population) of 2.08 (1.47–2.43), corresponding to an estimated 15,355 (10,852–17,938) cases.[22] About 4,000 people in England have motor neurone disease, of whom approximately 3200 will have ALS.[23] A recent meta-analysis demonstrated that mutations in the *SOD1* gene are responsible for approximately 14.8% of fALS, and 1.2% of sALS cases in Europe.[24] Using these figures (and assuming 90% of ALS cases are sporadic), there are estimated to be 82 people in England suffering from ALS who have mutations in the SOD1 gene.

Hospital admissions data for England in 2018-2019 recorded 4,328 finished consultant episodes (FCE) for MND (ICD 10: G12.2), 2,612 hospital admissions, 875 day cases and 24,607 FCE bed days.[25]

Approximately 50% of patients with ALS die within 30 months of symptom onset, often from respiratory insufficiency,[26,27] however about 10% of patients may survive for more than a decade.[28,29]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is no cure or standard treatment for MND. Symptomatic and supportive treatment can help people be more comfortable while maintaining their quality of life. Multidisciplinary clinics, with specialists from neurology, physical therapy, respiratory therapy, and social work are particularly important in the care of individuals with MNDs.[30]

Patients with a diagnosis of MND should have a team to assess, manage and review the following areas, including the person's response to treatment:[31]

- Weight, diet, nutritional and fluid intake, feeding and swallowing.
- Muscle problems, such as weakness, stiffness, cramps.
- Physical function, including mobility and activities of daily living.
- Saliva problems, such as drooling of saliva (sialorrhoea) and thick, tenacious saliva.
- Speech and communication.
- Cough effectiveness.
- Respiratory function and respiratory symptoms.
- Pain and other symptoms, such as constipation.
- Cognition and behaviour.
- Psychological support needs.
- Social care needs.
- End of life care needs.
- Information and support needs for the person and their family members and/or carers (as appropriate).

CURRENT TREATMENT OPTIONS

There is no cure for ALS, management consists of symptomatic and palliative care. Riluzole (Rilutek) is currently the only drug licensed for treating ALS in the UK. The licensed indication of riluzole is to extend life or the time to mechanical ventilation for individuals with ALS.[9]

PLACE OF TECHNOLOGY

If licenced, tofersen will offer a treatment option for patients with ALS (either sALS or fALS) caused by confirmed mutations in the SOD1 gene who currently have no effective therapies available.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	NCT02623699, EudraCT: 2015-004098-33; A Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BIIB067 Administered to Adult Subjects With Amyotrophic Lateral Sclerosis and Confirmed Superoxide Dismutase 1 Mutation **Phase I/II/III**	NCT03070119, EudraCT: 2016-003225-41; An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults With Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation **Phase III extension**

	Location(s): EU (including the UK), Canada, United States and other countries	**Location(s):** EU (including the UK), Canada, United States and other countries
Trial design	Randomised, parallel assignment (quadruple masking)	Non-randomised, sequential assignment (open label)
Population	N=183 (planned); subjects with a weakness attributable to ALS and documented SOD1 mutation; aged 18 yrs and older.	N=183 (planned); subjects must have a diagnosis of SOD1-ALS and must have completed the end of study visit for either parts A, B or C of NCT02623699; aged 18 yrs and older.
Intervention(s)	Tofersen administered as an intrathecal injection: • Experimental: Randomised single ascending dose (part A) • Experimental: Randomised multiple ascending dose (part B) • Experimental: Fixed dose (part C)	Participants receive a loading dose regimen followed by a maintenance dose.
Comparator(s)	Matched placebo	No comparator
Outcome(s)	Primary outcomes (time frame: part A [single-ascending dose] and B [multiple-ascending dose] – up to day 169): • Number of participants experiencing adverse events (AEs) and serious adverse events (SAEs) • Number of participants with significant abnormalities in clinical laboratory assessments, vital signs, physical and neurological examinations and 12-lead electrocardiograms abnormalities Primary and secondary outcomes (time frame: part C [Pivotal]: • Change from baseline in ALS functional rating scale-revised (ALSFRS-R) total score at week 28. There are 12 questions, each scored from 0 (no function) to 4 (full function). Total possible score is 48. ALSFRS-R scores calculated at diagnosis can be compared to scores throughout time to determine the speed of progression (timeframe: baseline to day 197). • Change from baseline in CSF levels of SOD1 protein (time frame: up to day 169]. • Change from baseline in slow vital capacity [time frame: baseline to day 197]. • Ventilation assistance-free survival [time frame: baseline to day 225]. • Overall survival [time frame: baseline to day 225]. • Change from baseline in muscle strength measured by handheld dynamometry [time frame: baseline to day 197]. • Number of participants experiencing AEs and SAEs [time frame: baseline to day 225].	Primary outcome (time frame: up to week 248): • Number of participants with AEs and SAEs. See trial record for full list of other outcomes.

	• Change from baseline in phosphorylated axonal neurofilament heavy chain (p-NFH) concentration in CSF [time frame: baseline to day 169]. See trial record for full list of other outcomes.	
Results (efficacy)	-	-
Results (safety)	-	-

ESTIMATED COST

The cost of tofersen is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology Appraisal guidance. Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease (TA20). January 2001.
- NICE guideline. Motor neurone disease: assessment and management (NG42). February 2016, updated July 2019.
- NICE quality standard. Motor neurone disease (QS126). July 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised rehabilitation for patients with highly complex needs (All ages). D02/S/a

OTHER GUIDANCE

Royal College of General Practitioners and Motor Neurone Disease Association. Motor neurone disease: a guide for GPs and primary care teams. 2018.[32]

ADDITIONAL INFORMATION

Biogen licensed tofersen from Ionis Pharmaceuticals, Inc. under a collaborative development and license agreement.[10]

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