NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Sodium phenylbutyrate-ursodoxicoltaurine for treating amyotrophic lateral sclerosis

Company/Developer	Amylyx Pharmaceuticals

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 20463	NICE TSID: 11816	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Sodium phenylbutyrate-ursodoxicoltaurine is currently in clinical development for amyotrophic lateral sclerosis (ALS), a form of motor neurone disease (MND). 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. There is currently no treatment to stop the progression of ALS.

Sodium phenylbutyrate-ursodoxicoltaurine is a coformulation of two compounds designed to reduce nerve cell death by blocking cell death pathways that originate in the endoplasmic reticulum and mitochondria, two cellular components. Sodium phenylbutyrate-ursodoxicoltaurine is administered orally or via feeding tube within 1 hour of preparation. Evidence shows that sodium phenylbutyrate-ursodoxicoltaurine is safe and effective even long-term. If licensed, sodium phenylbutyrate-ursodoxicoltaurine will offer an additional treatment option for people with ALS who currently have few effective therapies available.

Proposed Indication

Treatment of adults with amyotrophic lateral sclerosis (ALS).[1]

Technology

Description

Sodium phenylbutyrate is an inhibitor of histone deacetylases (HDACs) and ursodoxicoltaurine is a hydrophilic bile acid. Even though the exact mechanism of action of sodium phenylbutyrate-ursodoxicoltaurine is unknown, evidence from preclinical studies suggest that both drugs may act as chemical chaperones and inhibit apoptosis by ameliorating endoplasmic reticulum stress and preventing misfolded protein accumulation. In addition, sodium phenylbutyrate modulates chromatin remodelling and transcription by inhibiting the activity of HDACs and increasing histone acetylation, while ursodoxicoltaurine exerts neuroprotective activity by reducing oxidative stress and inhibiting Bax translocation to mitochondria.[2]

Sodium phenylbutyrate-ursodoxicoltaurine is currently in clinical development for treating ALS in adults.[1] The coformulation is available as a sachet, containing 3 g of sodium phenylbutyrate and 1g of ursodoxicoltaurine powder for oral suspension. The contents of each sachet are vigorously mixed with 250 mL or 8 oz of water at room temperature, and administered orally or via feeding tube within 1 hour of preparation. The recommended dosage is one sachet once daily for the first 3 weeks and one sachet twice daily thereafter.[2]

Key Innovation

Existing medical interventions for ALS are mainly symptomatic therapies for complications of amyotrophic lateral sclerosis. Specific drugs, such as riluzole and edaravone, work with very modest efficacy, only slightly limiting the progression of pathology.[3] The safety and efficacy of sodium phenylbutyrate and ursodoxicoltaurine was evaluated in a multicenter phase 2 trial (CENTAUR; NCT03127514) encompassing a 6- month randomized placebo-controlled phase and an open label extension long-term follow-up phase. At the end of 6 months, sodium phenylbutyrate-ursodoxicoltaurine significantly slowed decline on the ALS Functional Rating Scale Revised (ALSFRS-R) in participants with ALS. The treated group lost 1.24 points per month compared to 1.66 for placebo (p=0.03), which resulted in a between group difference of 2.32 points at the end of 6 months The benefit was independent of concomitant use of riluzole and/or edaravone.[4] Furthermore, longer-term treatment with sodium phenylbutyrate-ursodoxicoltaurine was associated with functional and survival benefits in analyses spanning the randomized and open-label extension phases. At week 48 (24 weeks randomized phase and 24 weeks open-label extension phase), estimated least squared mean ALSFRS-R total score, upper- and lower-limb ATLIS score and SVC was greater in participants originally randomized to sodium phenylbutyrate-ursodoxicoltaurine than those originally randomized to placebo, with between-group differences for the respective endpoints being 4.23 points.[2] If licensed, sodium phenylbutyrate-ursodoxicoltaurine will offer an additional treatment option for patients living with ALS who currently have few effective therapies available.

Regulatory & Development Status

Sodium phenylbutyrate-ursodoxicoltaurine does not currently have marketing authorisation in the EU/UK for any indication.

Sodium phenylbutyrate-ursodoxicoltaurine has the following regulatory designations/awards for ALS:[5,6]

- Orphan drug designation in the EU in 2020
- Orphan drug designation in the US in 2017

Patient Group

Disease Area and Clinical Need

Motor neurone disease (MND) is a rare disease that affects the brain and nerves, causing weakness that worsens over time.[7] ALS is a form of MND. ALS is a fatal neurodegenerative disease characterised by the loss of motor neurons in motor cortex and spinal cord, leading to progressive muscle degeneration, spasticity, dysphagia and neurocognitive symptoms; respiratory paralysis and death generally occurs within 3–5 years after diagnosis.[2] There are two main types of ALS; sporadic and familial. Nearly all cases of ALS are sporadic, which means the disease occurs randomly with no clearly associated risk factors or family history of the disease. The exact causes of sporadic are unknown but are believed to include genetic and environmental factors. About 5-10% of all ALS cases are familial, which means that an individual inherits the disease from one parent who carries the disease-causing gene. Mutations found in more than a dozen genes have been associated with the onset familial and sporadic ALS.[8] The initial symptoms of ALS can be quite varied. Symptoms can begin in the muscles that control speech and swallowing or in the hands, arms, legs or feet. Not all people with ALS experience the same symptoms or the same sequences or patterns of progression. However, progressive muscle weakness and paralysis are universally experienced. A gradual onset of progressive muscle weakness – which is generally painless – is the most common initial symptom in ALS. Other early symptoms vary but can include tripping, dropping things, abnormal fatigue of the arms and/or legs, slurred speech, muscle cramps and twitches, uncontrollable periods of laughing or crying and cognitive and behavioural changes.[9,10]

About 4,000 people in England have MND, of whom approximately 3,200 will have ALS.[11] In England, in 2021-22, there were 4,406 finished consultant episodes (FCE) for MND (ICD 10: G12.2), resulting in 2,694 hospital admissions and 21,826 FCE bed days.[12] ALS has a reported incidence of 1-2/100,000 person-years. 5000 people are estimated to have ALS in the UK at any one time; however, the true figure and geographical distribution, are unknown.[13] The proportion of people newly diagnosed with ALS annually in the UK was projected to rise from a baseline of 1,415 UK cases in 2010 to 1,701 in 2020 and 2,635 in 2116.The overall prevalence of ALS was predicted to increase from 8.58 per 100,000 persons in 2020 to 9.67 per 100,000 persons in 2116.[14]

Recommended Treatment Options

There is currently no cure for ALS and no effective treatment to halt or reverse the progression of the disease. Management of ALS consists of symptomatic and palliative care.[15] Riluzole is currently the only drug recommended for ALS by NICE. The licensed indication of riluzole is to extend life or the time to mechanical ventilation for individuals with ALS.[16]

Clinical Trial Information

Trial	**Phoenix; NCT05021536; EudraCT 2021-000250-26;** A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial to Evaluate the Safety and Efficacy of AMX0035 Versus Placebo for 48-week Treatment of Adult Patients With Amyotrophic Lateral Sclerosis (ALS) **Phase III –** Recruiting **Location(s):** 10 EU countries, UK and USA **Primary completion date:** November 2023
Trial Design	Randomised, parallel assignment, quadruple-blinded

Population	N=600 (estimated); adults who have diagnosis of ALS (definite or clinically probable)
Intervention(s)	Oral sodium phenylbutyrate-ursodoxicoltaurine
Comparator(s)	Matching placebo
Outcome(s)	Primary outcome measures: • Joint assessment of ALSFRS-R total score progression over 48 weeks adjusted for mortality [Time Frame: 48 weeks] • Number of Participants With Adverse Events [Time Frame: 48 weeks] • Number of Participants in Each Group Able to Remain on Study Drug Until Planned Discontinuation [Time Frame: 48 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**CENTAUR**; NCT03127514 Evaluation of the Safety, Tolerability, Efficacy and Activity of AMX0035, a Fixed Combination of Phenylbutyrate (PB) and Tauroursodeoxycholic Acid (TUDCA), for the Treatment of ALS **Phase II** – Completed **Location(s):** USA **Study completion date:** November 2019	**CENTAUR-OLE**; NCT03488524; Open Label Extension Study of AMX0035 in Patients With ALS **Phase II** – Completed **Location(s):** USA **Study completion date:** November 2021
Trial Design	Randomised, parallel assignment, quadruple-blinded	Single group assignment, open-label extension study
Population	N=137 (actual); adults who have Sporadic or familial ALS diagnosed as definite as defined by the World Federation of Neurology revised El Escorial criteria	N=95 (actual); subjects who completed all visits in the randomized, double blind AMX0035 study. Subjects that receive tracheostomy or PAV during the course of the main study were still followed as ITT until the week 24 visit before enrolment in the OLE
Intervention(s)	Oral sodium phenylbutyrate-ursodoxicoltaurine	
Comparator(s)	Matching placebo	No comparator
Outcome(s)	Primary outcome measures: • Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R)	Primary outcome measure: Quantity of adverse events and serious adverse events observed in the study [Time Frame: 30 months].

	Slope Change [Time Frame: 24 Weeks] • Number of Participants With Adverse Events [Time Frame: 24 Weeks] • Number of Participants in Each Group Able to Remain on Study Drug Until Planned Discontinuation [Time Frame: 24 weeks] See trial record for full list of other outcomes.	See trial record for full list of other outcomes.
Results (efficacy)	See trial record	"Risk of any key event (all-cause death, tracheostomy/permanent assisted ventilation, and first hospitalization) was 47% lower in those originally randomised to PB and TURSO (n=87) versus placebo (n=48, 71% of whom received delayed-start PB and TURSO in the OLE phase) (HR=0.53; 95% CI 0.35 to 0.81; p=0.003)."[17]
Results (safety)	See trial record	"Longer-term, the tolerability profle of sodium phenylbutyrate/ursodoxicoltaurine did not reveal new safety signals. In the CENTAUR-OLE (NCT03488524), the most commonly reported AEs included falls (19%), nausea (14%) and diarrhoea (13%), which were consistent with symptoms of ALS progression (e.g. respiratory failure, falls) or AEs most commonly reported with sodium phenylbutyrate/ursodoxicoltaurine during the CENATUAR trial (e.g. gastrointestinal symptoms)".[2]

Clinical Trial Information	
Trial	NCT04987671; A Pharmacokinetic and Pharmacodynamic Study of AMX0035 in Patients With ALS **Phase I/II –** Active, not recruiting **Location(s):** USA **Primary completion date:** May 2022
Trial Design	Single group assignment, open-label
Population	N=14 (estimated); adults who have diagnosis of sporadic ALS (definite, probable, laboratory probable, possible) made by physician experienced with management

	of ALS as defined by the World Federation of Neurology revised El Escorial criteria
Intervention(s)	Oral sodium phenylbutyrate-ursodoxicoltaurine
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Blood concentration of PB and taurursodiol [Time Frame: Between Day 1 and Day 40] • Systemic exposure to PB and taurursodiol [Time Frame: Between Day 1 and Day 40] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of sodium phenylbutyrate-ursodoxicoltaurine is not yet known.

Relevant Guidance

NICE Guidance

- NICE Technology Appraisal guidance in development. Tofersen for treating amyotrophic lateral sclerosis caused by SOD1 gene mutations (GID-HST10050). Expected date of issue to be confirmed.
- 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.[18]

Additional Information

Amylyx Pharmaceuticals 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.

References

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