Sodium Phenylbutyrate and Ursodoxicoltaurine: First Approval

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Abstract
An oral, fixed-dose coformulation of sodium phenylbutyrate and ursodoxicoltaurine (ALBROZIA™; hereafter denoted sodium phenylbutyrate/ursodoxicoltaurine) is being developed by Amylyx Pharmaceuticals for the treatment of neurodegenerative diseases. In June 2022, the coformulation received its first approval with conditions in Canada for the treatment of amyotrophic lateral sclerosis (ALS) in adults. The approval was based on results from the multicentre, phase II CENTAUR trial, in which slowing of ALS progression was demonstrated with sodium phenylbutyrate/ursodoxicoltaurine relative to placebo. This article summarizes the milestones in the development of sodium phenylbutyrate/ursodoxicoltaurine leading to this first approval.

Sodium phenylbutyrate and ursodoxicoltaurine (ALBROZIA™): Key points

- An oral fixed-dose coformulation being developed by Amylyx Pharmaceuticals for the treatment of neurodegenerative diseases
- Received its first approval with conditions on 13 June 2022 in Canada
- Approved for the treatment of ALS in adults

1 Introduction
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized 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 [1, 2]. Although the pathophysiology of ALS is largely unknown, several altered signaling mechanisms, such as mitochondrial dysfunction, endoplasmic reticulum stress, hyperexcitability, impaired protein homeostasis, oxidative stress and neuroinflammation have been recognized as potential pathogenic factors in ALS [1, 2].

On 13 June 2022, sodium phenylbutyrate/ursodoxicoltaurine received its first approval with conditions in Canada for the treatment of ALS in adults [3, 4]. The approval was authorized under Health Canada’s Notice of Compliance with Conditions policy, with one of the conditions being the provision of data from the ongoing phase 3 PHOENIX trial (NCT05021536); other conditions include additional planned or ongoing studies [3]. The coformulation is available as a sachet, containing 3 g of sodium phenylbutyrate and 1 g of ursodoxicoltaurine powder for oral suspension [4]. 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 h of preparation. The recommended dosage of sodium phenylbutyrate/ursodoxicoltaurine is one sachet once daily for the first 3 weeks and one sachet twice daily thereafter. If the proposed dosage of one sachet twice daily is not tolerated, dosage may be reduced...
Sodium phenylbutyrate/ursodoxicoltaurine should be taken before a meal, especially in patients with low body weight (< 70 kg). Its use is contraindicated during pregnancy and breastfeeding [4].

Sodium phenylbutyrate/ursodoxicoltaurine is undergoing regulatory review in the USA and EU for the treatment of ALS. In the USA, the coformulation is also undergoing phase II clinical development for Alzheimer’s disease and preclinical development for Wolfram syndrome.

1.1 Company Agreements

Amylyx Pharmaceuticals received funding from various sources for sodium phenylbutyrate/ursodoxicoltaurine. In November 2015, Amylyx Pharmaceuticals received funding from the ALS Finding a Cure Foundation and the Cure Alzheimer’s Fund to support the clinical development of sodium phenylbutyrate/ursodoxicoltaurine [5]. In July 2016, the ALS Association and the ALS Finding a Cure® jointly provided funding to support a phase II trial of sodium phenylbutyrate/ursodoxicoltaurine in ALS [6]. Later that year in August 2016, Amylyx Pharmaceuticals announced that it had completed a $5 million Series A financing to support the phase II trial [7]. In October 2017, the Alzheimer’s Association and Alzheimer’s Drug Discovery Foundation granted funding to support a phase II trial of sodium phenylbutyrate/ursodoxicoltaurine in participants with Alzheimer’s disease [8].

An oversubscribed Series B financing led by Morningside Venture and Series C financing led by Viking Global Investors to support the clinical development and potential launch plans for sodium phenylbutyrate/ursodoxicoltaurine for the treatment of ALS, Alzheimer’s disease and other neurodegenerative diseases has been closed in July 2020 [9] and July 2021 [10], respectively.

2 Scientific Summary

2.1 Pharmacodynamics

The exact mechanism of action of sodium phenylbutyrate/ursodoxicoltaurine is unknown, but the coformulation may reduce neuronal cell death in vitro [4]. Sodium

![Chemical structure of sodium phenylbutyrate and ursodoxicoltaurine](image-url)
phenylbutyrate is an inhibitor of histone deacetylases (HDACs) and ursodoxicoltaurine is a hydrophilic bile acid [11–13]. 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 remodeling 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. Sodium phenylbutyrate and ursodoxicoltaurine exhibit anti-inflammatory properties in several animal neurodegeneration models [11–13].

Sodium phenylbutyrate and ursodoxicoltaurine have been shown to reduce neuronal death and other pathological features in several animal models of neurodegenerative disease, including ALS [12, 13]. In vitro, the combination of sodium phenylbutyrate and ursodoxicoltaurine demonstrated a greater and distinct impact in regulating gene expressions involved in ALS-relevant pathways (e.g. nucleocytoplasmic transport, unfolded protein response, mitochondrial function and immune activation) compared with each drug administered alone [11].

In the phase II PEGASUS trial (NCT03533257; Sect. 2.3.2), sodium phenylbutyrate/ursodoxicoltaurine demonstrated a significant impact on multiple neurological biomarkers of interest in Alzheimer’s disease [14]. After 24 weeks of treatment, the level of core Alzheimer’s disease biomarkers (i.e. amyloid β species, total tau and phospho-tau 181 in cerebrospinal fluid) significantly (p < 0.05) improved from baseline with sodium phenylbutyrate/ursodoxicoltaurine compared with placebo [14].

2.2 Pharmacokinetics

Following a single dose administration of oral sodium phenylbutyrate/ursodoxicoltaurine 3 g/1 g in healthy subjects in fasted conditions, sodium phenylbutyrate was rapidly absorbed and reached a mean maximum concentration (Cmax) of 188 µg/mL in a median time of 1 h, while ursodoxicoltaurine reached a mean Cmax of 871 ng/mL in a median time of 4.5 h [4]. The plasma concentration profile of ursodoxicoltaurine had two to three peaks in many participants, which was consistent with storage and release of bile acids after a meal/snack under physiological condition. Based on a population pharmacokinetic analysis, the estimated steady-state mean Cmax of sodium phenylbutyrate in participants with ALS was 131 µg/mL. There is no or little accumulation of sodium phenylbutyrate and ursodoxicoltaurine after once- or twice-daily administration [4].

In healthy subjects, administration of oral sodium phenylbutyrate/ursodoxicoltaurine 3 g/1 g with a high-fat, high-calorie meal decreased sodium phenylbutyrate Cmax and area under the curve (AUC) by 75% and 55%, respectively [4]. A high-fat, high-calorie meal did not affect ursodoxicoltaurine Cmax, but increased AUC by 46% [4].

In vitro, plasma protein binding of sodium phenylbutyrate and ursodoxicoltaurine was 82% and 98%, respectively [4]. Sodium phenylbutyrate is rapidly metabolized to phenylacethylate, the primary metabolite that may have pharmacological activity, and conjugated with glutamine via acetylation in the liver and kidney to form phenylacetylglutamine. Ursodoxicoltaurine, a naturally occurring hydrophilic bile acid, is subject to extensive enterohepatic recirculation, which results in active deconjugation of ursodoxicoltaurine to ursodiol (UDCA) by intestinal microflora, and reconjugation of UDCA with glycine or taurine to form glyco/tauroxycholic acid and ursodoxicoltaurine, respectively, in the liver [4].

Following a single dose administration of oral sodium phenylbutyrate/ursodoxicoltaurine 3 g/1 g in healthy subjects in fasted conditions, estimated half-life of sodium phenylbutyrate, phenylacetate and ursodoxicoltaurine was 0.46, 0.81 and 4.34 h, respectively [4]. The majority (≥80–100%) of administered sodium phenylbutyrate is excreted in the urine within 24 h as phenylacetylglutamine. Following ursodoxicoltaurine administration, the levels of UDCA in faeces are known to be increased [4].

Sex and age had no consistent discernable effects on the pharmacokinetics of sodium phenylbutyrate and ursodoxicoltaurine [4]. The impact of race, and impaired kidney or hepatic function on the pharmacokinetics of sodium phenylbutyrate/ursodoxicoltaurine are unknown due to limited or lack of data. Given that sodium phenylbutyrate and ursodoxicoltaurine are metabolized in the liver and kidney, caution is warranted when the coformulation is administered in patients with impaired kidney or hepatic function [4].

In vitro, sodium phenylbutyrate/ursodoxicoltaurine inhibits CYP1A2, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP2B6, and CYP3A4 isoenzymes and may therefore increase exposure to drugs that are metabolized by these CYP450 enzymes [4]. Subsequently, coadministration of sodium phenylbutyrate/ursodoxicoltaurine with these CYP450 substrates with narrow therapeutic indices should be avoided. Concomitant use of sodium phenylbutyrate/ursodoxicoltaurine with bile acid sequestering agents (may interfere with ursodoxicoltaurine absorption), probenecid (may affect renal excretion of sodium phenylbutyrate) and HDAC inhibitors [may lead to excess inhibition of HDAC and increase the incidence of class-specific adverse events (AEs)] should also be avoided. In addition, drug-drug interactions are possible when sodium phenylbutyrate/ursodoxicoltaurine is coadministered with other agents, including aluminum-based antacids, bile salt influx pump inhibitors, enzyme-inducing antiepileptic drugs and OAT1 substrates [4]. Local prescribing information should be consulted for further details.
2.3 Therapeutic Trials

2.3.1 Amyotrophic Lateral Sclerosis

Sodium phenylbutyrate/ursodoxicoltaurine slowed ALS progression in a 24-week, randomized, double-blind, placebo-controlled, multicentre phase II trial (CENTAUR; NCT03127514) [15]. Participants aged 18–80 years with definite ALS (defined by the revised El Escorial criteria) who had symptom onset within 18 months were randomized to receive one sachet of sodium phenylbutyrate/ursodoxicoltaurine 3 g/1 g (n = 89) or placebo (n = 48) once daily for 3 weeks and, if tolerated, one sachet twice daily thereafter. The contents of sachet were administered orally or through a feeding tube. Concomitant use of riluzole (participants had to be on a stable dose for ≥ 30 days prior to screening) and/or edaravone was allowed during the trial. Participants who completed the trial on study drug were eligible to enroll in an open-label extension phase (CENTAUR-OLE; NCT03488524) to receive sodium phenylbutyrate/ursodoxicoltaurine for up to 132 weeks [15].

After 24 weeks of treatment, the study met its primary endpoint, with the rate of decline in the total score on the ALS Functional Rating Scale-Revised (ALSFRS-R; range 0–48 with higher scores indicative of better function) being significantly slower with sodium phenylbutyrate/ursodoxicoltaurine than with placebo (−1.24 vs −1.66 points per month respectively; p = 0.03); the between-group difference in the total ALSFRS-R score was 2.32 points at week 24 [15]. At this time point, there were no significant differences between the groups in terms of secondary endpoints, which include the rate of decline in isometric muscle strength and respiratory function (assessed by the Accurate Test of Limb Isometric Strength (ATLIS) device) and the slow vital capacity (SVC), respectively], the change in phosphorylated axonal neurofilament H subunit levels, and the time to death, tracheostomy, permanent assisted ventilation (PAV), and/or hospitalizations. The efficacy of sodium phenylbutyrate/ursodxicoltaurine was unaffected by concomitant use of riluzole and/or edaravone [15].

Longer-term treatment with sodium phenylbutyrate/ursodxicoltaurine was associated with functional and survival benefits in analyses spanning the randomized and open-label extension phases [16–19]. 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 (n = 56) than those originally randomized to placebo (n = 34), with between-group differences for the respective endpoints being 4.23 points (95% CI 0.56–7.90; p = 0.02), 7.83 points (0.85–14.80; p = 0.03), 4.74 points (−3.00 to 12.48; p = 0.23) and 10.66% (0.63–20.69; p = 0.04) [18]. In the final intent-to-treat overall survival analysis (cutoff date July 2020; longest follow-up of 35 months after randomization), the median overall survival was 25.8 months in participants originally randomized to sodium phenylbutyrate/ursodxicoltaurine versus 18.9 months in those originally randomized to placebo (n = 34), with between-group differences for the respective endpoints being 4.23 points (95% CI 0.56–7.90; p = 0.02), 7.83 points (0.85–14.80; p = 0.03), 4.74 points (−3.00 to 12.48; p = 0.23) and 10.66% (0.63–20.69; p = 0.04) [18]. In the final intent-to-treat overall survival analysis (cutoff date July 2020; longest follow-up of 35 months after randomization), the median overall survival was 25.8 months in participants originally randomized to sodium phenylbutyrate/ursodxicoltaurine versus 18.9 months in those originally randomized to placebo [hazard ratio (HR) 0.57; 95% CI 0.35–0.92; p = 0.023] [17]. Furthermore, the risk of any key event (i.e. all-cause death, tracheostomy, PAV, and hospitalizations), tracheostomy/PAV or death, or first hospitalization was significantly (p ≤ 0.03) lower in participants originally randomized to sodium phenylbutyrate/ursodxicoltaurine versus placebo by 47% (HR 0.53; 95% CI 0.35–0.81), 49% (0.51; 0.32–0.84) and 44% (0.56; 0.34–0.95), respectively [16]. The beneficial effects

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of sodium phenylbutyrate/ursodoxicoltaurine over placebo were consistent regardless of concomitant use of riluzole, edaravone, or both at baseline [19].

Post hoc subgroup analysis based on originally randomized group in the CENTAUR trial and enrollment in the CENTAUR-OLE demonstrated that earlier and longer exposure to sodium phenylbutyrate/ursodoxicoltaurine was associated with longer median survival duration [17].

2.3.2 Alzheimer’s Disease

A 24-week, randomized, double-blind, placebo-controlled multicentre phase II trial (PEGASUS; NCT03533257) evaluated the safety, neurobiological activity and preliminary efficacy of sodium phenylbutyrate/ursodoxicoltaurine in participants aged 55–89 years with probable Alzheimer’s disease or mild cognitive impairment with biomarkers supporting Alzheimer’s disease pathology \((n = 95)\) [14, 20]. Participants were randomized to receive sodium phenylbutyrate/ursodoxicoltaurine or placebo for 24 weeks; participants in stable dose regimen were allowed to use standard-of-care medications for Alzheimer’s disease during the trial. After 24 weeks of treatment, there was no significant difference between the sodium phenylbutyrate/ursodoxicoltaurine and the placebo groups in change from baseline in the composite outcome of cognitive, functional and imaging measures, as assessed by Mild/Moderate Alzheimer’s Disease Composite Scale, Functional Activities Questionnaire and hippocampal volumetric magnetic resonance imaging (primary efficacy outcome). However, it should be noted that the trial was not powered to determine between-group differences in efficacy outcomes [14, 20].

2.4 Adverse Events

Sodium phenylbutyrate/ursodoxicoltaurine was generally well tolerated during the CENTAUR trial (NCT03127514) in participants with ALS [4, 15]. The most common AEs occurring in \(\geq 5\%\) of sodium phenylbutyrate/ursodoxicoltaurine recipients \((n = 89)\) and at a higher incidence than in placebo recipients \((n = 48)\) included diarrhoea \((18\% \text{ vs } 10\%)\), abdominal pain \((10\% \text{ vs } 2\%)\), nausea \((9\% \text{ vs } 4\%)\), constipation \((8\% \text{ vs } 4\%)\), fatigue \((8\% \text{ vs } 2\%)\), decreased appetite \((7\% \text{ vs } 4\%)\) and dizziness \((6\% \text{ vs } 2\%)\) [4]. The most common laboratory abnormalities \((\geq 5\%)\) in the sodium phenylbutyrate/ursodoxicoltaurine group included proteinuria \((6\% \text{ vs } 4\%)\) and ketonuria \((5\% \text{ vs } 2\%)\) [4]. Gastrointestinal AEs were more common with sodium phenylbutyrate/ursodoxicoltaurine in the first 3 weeks of treatment initiation [4, 15].

Serious AEs occurred in 12% of sodium phenylbutyrate/ursodoxicoltaurine recipients compared with 19% of placebo recipients, and most were not considered to be treatment-related [15]. Dose interruption, dose reduction or treatment discontinuation due to an AE occurred in 15%, 4% and 19% of participants in the sodium phenylbutyrate/ursodoxicoltaurine group versus 12%, 0% and 8% of participants in the placebo group, with diarrhoea and respiratory failure being the most common AE leading to treatment discontinuation in the respective groups. Death was reported in five \((6\%)\) sodium phenylbutyrate/ursodoxicoltaurine recipients and two \((4\%)\) placebo recipients; the most common cause of death was respiratory failure, which was consistent with the natural progression of ALS [15].

Longer-term, the tolerability profile 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) [4, 18].

The overall tolerability profile of sodium phenylbutyrate/ursodoxicoltaurine in the PEGASUS trial

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(NCT03533257) in participants with Alzheimer’s disease was similar to that observed in participants with ALS [14]. According to data from the CENTAUR and PEGASUS trials, most AEs with sodium phenylbutyrate/ursodoxicoltaurine were mild to moderate in severity and unrelated to treatment [21]. The incidence of cardiac events (e.g., atrial fibrillation, atrioventricular block first degree, bundle branch block left, left anterior hemiblock, palpitations, tachycardia and intraventricular conduction delay [4]) associated with sodium phenylbutyrate/ursodoxicoltaurine occurred in 8% of participants with ALS and 4% of participants with Alzheimer’s disease, and no clinically meaningful electrocardiographic changes were observed in both trials [22].

2.5 Ongoing Clinical Trials

The randomized, double-blind, placebo-controlled, multicentre phase III PHOENIX trial (NCT05021536) is currently recruiting participants to evaluate the efficacy and safety of sodium phenylbutyrate/ursodoxicoltaurine for the treatment of ALS in a broader, international population [23]. An intermediate size Expanded Access Program (NCT05286372) is available to provide expanded access to sodium phenylbutyrate/ursodoxicoltaurine in participants living with ALS in the USA who are not eligible for ALS clinical trials. The program also aims to assess the safety of the coformulation in diverse population and/or stages of ALS. Moreover, an open-label, compassionate extended-use protocol (NCT04516096) is ongoing for participants who have completed their participation in a clinical trial sponsored by Amylyx Pharmaceuticals for the treatment of ALS; the trial is intended to provide extended treatment with sodium phenylbutyrate/ursodoxicoltaurine. Recruitment is also underway in a phase I/II trial (NCT04987671) to evaluate the pharmacodynamic and pharmacokinetic effects of single or multiple doses of sodium phenylbutyrate/ursodoxicoltaurine in participants with sporadic ALS.

3 Current Status

Sodium phenylbutyrate/ursodoxicoltaurine received its first approval with conditions on 13 June 2022 for the treatment of ALS in adults in Canada [3].

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Declarations

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