

CADTH Horizon Scan

Emerging Drugs for Amyotrophic Lateral Sclerosis

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Key Messages

- Horizon scan reports provide brief summaries of information regarding new and emerging health technologies. These technologies are identified through the CADTH Horizon Scanning Service as topics of potential interest to health care decision-makers in Canada. This Horizon Scan summarizes the available information regarding emerging drug therapies for the treatment of patients with amyotrophic lateral sclerosis.
- Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurodegenerative disorder characterized by muscle weakness and wasting. ALS can be classified as sporadic (sALS), which accounts for 85% to 90% of the cases, or familial (fALS), which includes 10% to 15% of the cases.
- At present, 2 drugs are available in Canada for the treatment of patients with ALS, riluzole and edaravone. These 2 drugs provide modest benefits in terms of survival and function.
- Many treatments are currently in various stages of clinical development. Fasudil, ibudilast, inosine, and masitinib are drugs of interest as they have completed phase II, and some have initiated phase III, of their respective clinical development. Several other drugs are in clinical development and are briefly described in this report: AT-1501, CNM-Au8, engensis, pridopidine, verdiperstat, and zilucoplan.
- Emerging drugs for ALS pertain to different drug classes. Despite different mechanisms of action, these drugs all aim at providing a neuroprotective effect that will result in slowing of disease progression, maintenance of patient functional status, and improvement in patient survival.
- Of the 4 ALS drugs of interest in late-stage development, fasudil, ibudilast, and inosine have completed phase II of clinical development.
- The estimated completion date for phase III of clinical development for masitinib is December 2022.

Methods

These bulletins are not systematic reviews and do not involve critical appraisal or include a detailed summary of study findings. Rather, they present an overview of the technology and available evidence. They are not intended to provide recommendations for or against a particular technology.

Literature Search Strategy

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology (HTA) agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were amyotrophic lateral sclerosis (ALS) and inosine, masitinib, EH301, nicotinamide and pterostilbene, pterostilbene, AT-1501, engensis, fasudil, ibudilast, zilucoplan, verdiperstat, CNM-Au8, pridopidine (Table 1). No filters were applied to limit the retrieval by study type. The search was also not limited by language or by publication year. Regular alerts updated the search until project completion; only citations retrieved before December 1, 2021, were incorporated into the analysis.

Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was 1 of the drugs listed in Table 1. Conference abstracts and grey literature were included when they provided additional information to available published studies.

Peer Review

A draft version of this bulletin was reviewed by a clinical expert. The manufacturers were also given the opportunity to comment on an earlier draft.

Background

ALS, also known as Lou Gehrig’s disease and motor neuron disease,^{1,2} is a progressive fatal neurodegenerative disorder.^{3,4} In 70% of patients, ALS is characterized by limb-onset (initial weakness and wasting of arm or leg muscles); whereas 25% of patients have bulbar-onset (initial difficulty swallowing and slurring of speech), and the remaining patients (5%) have trunk-onset (respiratory involvement).^{3,4} Sporadic ALS (sALS) often occurs in those with no family history and accounts for 85% to 90% of the cases. Familial ALS (fALS) occurs when at least 2 persons of the same family are diagnosed and accounts for 10% to 15% of ALS cases.⁴ The lack of difference in the clinical symptoms between sALS and fALS patients may indicate a common molecular mechanism as the basis of this disease.⁴

ALS diagnosis is based on medical history, physical examination, electro-diagnostic testing, and neuroimaging studies. ALS may be difficult to differentiate from other conditions such as myasthenia gravis or multiple sclerosis.¹ The time from symptom onset to ALS diagnosis can vary from 9 to 12 months⁵ or in some cases up to 24 months.⁶

Table 1: Drugs Included in the Literature Search

| Drug | Development name | Sponsor |
|--|------------------|--------------------------------------|
| – | AT-1501 | Eledon Pharmaceuticals |
| Engensis | VM202 | Helixmith Co., Ltd. |
| Fasudil | – | University Medical Center Goettingen |
| Ibudilast | MN-166 | MediciNova |
| Inosine | – | Massachusetts General Hospital |
| Masitinib | – | AB Science |
| Nicotinamide riboside and pterostilbene | EH301 | Haukeland University Hospital |
| Drugs from the HEALEY ALS Platform Trial (4 arms): <ul style="list-style-type: none"> • Zilucoplan • Verdiperstat • CNM-Au8 • Pridopidine | – | Massachusetts General Hospital |

In Canada, it is estimated that about 3,000 persons are currently living with ALS.⁷ A meta-analysis has estimated the pooled ALS annual standardized incidence for Europe, New Zealand and North America to be 1.81 of 100,000.⁸ Studies have estimated the prevalence of ALS to be 4.1 to 8.4 per 100,000 persons.⁶ Commonly cited estimates of the global prevalence of ALS vary between 200,000² and 235,000 persons,⁹ though estimates as low as 55,000¹⁰ and as high as 500,000 persons¹¹ have also been reported. There is a projected 69% increase in the prevalence of this condition by year 2040.⁹

The mean age of onset of symptoms is 58 years to 63 years for sALS and 40 years to 60 years for fALS.³ Men have a higher risk of sALS with limb-onset than women (global sex ratio of 1.2 to 1.5).³ Prognosis is poor; the mean survival time from symptom onset to death or invasive respiratory support is between 24 months and 50 months.⁶ Some patients (about 10%) will have a survival of 10 years or longer.⁶

It is generally accepted that both genetic and non-genetic factors play a role in the pathogenesis of ALS.⁴ Non-genetic risk factors for ALS include being male and older age.^{3,6} Other possible risk factors include smoking, body mass index, physical inactivity, exposures to metals, pesticides, b-methylamino-L-alanine, head injury, and viral infections.³ At least 20 gene mutations have been implicated in ALS, including mutations in superoxide dismutase 1 (SOD1)(15% to 20% of fALS and 3% of sALS), TAR DNA binding protein (4% of fALS and 1% of sALS), and C9orf72 (5% of sALS and 30% of fALS).⁴

There is no cure for ALS.¹ Clinical management of ALS includes symptom, respiratory, and nutritional management.¹ Two drugs, riluzole and edaravone, are available in Canada for the treatment of ALS and may provide modest benefits.⁷ Riluzole may delay time to death or time to tracheostomy by approximately 3 months. Edaravone may delay functional decline, particularly when the treatment is initiated in patients with early disease.¹² As there is a need for improved therapeutics for patients with ALS, many drug treatments are in clinical development.^{13,14,12,15} The purpose of this report is to provide an overview of emerging drug molecules that are currently in advanced clinical development. Of note, the combination of sodium phenylbutyrate and taurursodiol (also known as tauroursodeoxycholic acid or AMX0035) is currently [under review](#) by CADTH and will therefore not be reviewed in this report.

The Technologies

A total of 11 drugs were initially identified and included in the literature search (Table 1). Table 2 provides a short description of the mechanism of action of 4 identified drugs of interest. Drugs that have not completed phase II of their clinical development were excluded from the main review and are discussed in the Concurrent Development section and Appendix 1.

Regulatory Status

Drugs described in Table 2 are not currently available in Canada. Of interest, in 2018 the Committee for Medicinal Products for Human Use of the European Medicine Agency (EMA)

recommended the refusal of the marketing authorization for Alsitek (masitinib) for the treatment of ALS since masitinib was deemed not effective at slowing disease progression based on interim results from phase II/III study AB10015.²² Final results⁹ as well as new overall survival data from this study have since become available.²³ In addition, a phase III clinical trial of masitinib for the treatment of patients with ALS, in combination with riluzole, was targeted for completion in December 2022.²⁴ However, masitinib's development was temporarily halted in 2021 due to safety concerns.^{25,26}

Cost

There is no cost information currently available.

Target Population

The population targeted for the use of the new emerging drugs described in this report is adults with ALS, which includes approximately 3,000 persons in Canada.⁷

Table 2: Emerging Drugs of Interest for the Treatment of ALS

| Drug | Mechanism of action and route of administration |
|--------------------|---|
| Fasudil | Fasudil is a ROCK inhibitor. In the treatment of ALS, this molecule is expected to be promote neuroprotection, induce axonal regeneration as well as improve survival and behavioural outcome. Fasudil is administered IV. ¹⁶ |
| Ibudilast (MN-166) | Ibudilast is an inhibitor of macrophage migration inhibitory factor and phosphodiesterases (3,4,10, and 11). This inhibition attenuates microglial activation and secretion of pro-inflammatory cytokines in the central nervous system. Persons with ALS have increased microglial activation in the motor cortices. Ibudilast is thought to be neuroprotective by suppressing neuronal cell death induced by microglial activation. ¹⁷ Ibudilast is administered orally. ¹⁸ |
| Inosine | Inosine is a urate precursor. Oxidative stress may play a role in the pathophysiology of ALS. Urate, through its antioxidant properties, may defend against oxidative stress and is thought to be neuroprotective in ALS. Inosine is administered orally. ¹⁹ |
| Masitinib | Masitinib is a tyrosine kinase inhibitor that targets mast cells and macrophages involved in inflammation and chronic inflammatory states. ²⁰ Masitinib is expected to provide neuroprotection in ALS by slowing microglial-related disease progression, reducing neuro-inflammation, and modulating the neuronal microenvironment in both central and peripheral nervous systems. ²¹ Masitinib is administered orally. ^{20,21} |

ALS = amyotrophic lateral sclerosis; C5 = complement component 5; CD40L = CD40 ligand; HGF = hepatocyte growth factor; NAD = nicotinamide adenine dinucleotide; ROCK = rho kinase.

Current Practice

While there are no formal ALS clinical practice guidelines in Canada, the first Canadian Best Practice Recommendations on the Management of ALS were recently developed.⁷ Reflecting the multiple needs of patients with ALS, these recommendations cover a broad range of topics including, the communication of the diagnosis of ALS, the use of disease-modifying therapies (riluzole and edaravone), and the need for patients to access multidisciplinary clinics. Other key aspects include nutritional interventions (e.g., enteral tube insertion) and respiratory care, in particular the use of non-invasive ventilation. The management of symptoms is also important, in particular the need to assess pain regularly and tailor pain control interventions toward the multiple specific causes of pain.⁷

Two drugs are presently available in Canada; riluzole and edaravone.⁷ They provide modest benefits in terms of survival (riluzole) and function (edaravone).¹² Riluzole is administered orally twice daily. It may extend survival and/or time to tracheostomy in some patients with ALS. There is no evidence that riluzole exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms; the drug has not been shown to be effective in the late stage of ALS.²⁷ Edaravone is indicated to slow the loss of function in patients with ALS, as measured by the ALSFRS-R scale. Edaravone is administered IV as a 1-hour infusion following a schedule involving an initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period. Subsequent treatment cycles are administered daily for 10 days out of 14-day periods, followed by 14-day drug-free periods.²⁸ Of note, an oral formulation of edaravone is being developed and is soon expected to complete its phase III clinical development.²⁹

Summary of the Evidence

Evidence currently available on emerging drugs of interest to this report initially included 26 relevant publications retrieved through the literature search. Among these, there were 17 conference abstracts and 9 full-text articles. Full-text articles report results from 7 trials, 2 sets of case reports, and 1 study protocol. Table 3 describes the number of, and type of publications retrieved for each of the 11 emerging drugs that were initially of interest and the inclusion, or exclusion, of publications based on the selection criteria. After further screening the publications retrieved, 13 conference abstracts and 6 full-text articles were included. Early emergent drugs without completed phase II trials or higher are excluded and discussed in the Concurrent Development section and in Appendix 1.

Fasudil

There are 2 registered clinical trials of fasudil for the treatment of patients with ALS. The first 1, completed in May 2015, was a phase II open-label, single-centre, clinical trial. The control group was composed of placebo patients from historical research (NCT01935518).⁵⁵ Results were presented in the form of an abstract at the 26th International Symposium on ALS/ Motor Neuron Disease.³⁰ The objective was to determine whether fasudil is effective and safe in treating patients with ALS. The key study entry criteria included a clinical diagnosis of laboratory-supported probable, probable, or definite ALS; disease duration of 3 to 36 months; forced vital capacity (FVC) of at least 60% of predicted, and an Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) score of at least 30 (respiratory items: at least

10) with decline in the 3 months preceding enrolment varying from 1 to 8. Patients also had to be taking riluzole.^{55,30} Of note, ALSFRS-R is a validated rating scale that measures the global function of patients with ALS. The total score varies from 0 (worst) to 48 (best).⁵¹ During the study, all patients were treated with IV fasudil 30 mg twice a day for 14 days; this treatment was repeated 3 months later. The primary and secondary outcome measures were the slope

Table 3: Publications retrieved from the literature search

| Drug | Type of publication | Evidence summary of inclusion or exclusion |
|---|--|---|
| Included | | |
| Fasudil | Two publications retrieved including a conference abstract ³⁰ and 1 full article describing the compassionate use of fasudil in 3 ALS patients. ³¹ | Included as phase II trial completed (compassionate use data excluded given availability of phase II data). |
| Ibudilast (MN-166) | Seven publications retrieved including 6 conference abstracts ³²⁻³⁷ and 1 full article reporting on an open-label, safety and PD trial. ¹⁷ | Included as phase II trial completed (phase I/II trial data excluded given availability of phase II data). |
| Inosine | Two publications retrieved including a conference abstract ³⁸ and a full article reporting on a pilot open-label trial. ³⁹ | Included as phase II trial completed (phase I trial data excluded given availability of phase II trial data). |
| Masitinib | Nine articles retrieved including 6 conference abstracts, ⁴⁰⁻⁴⁵ 1 full article reporting on a phase II/III RCT, ⁹ 1 full article reporting on a long-term survival analysis from the aforementioned phase II/III trial, ^{23,45} and 1 full article reporting on a hepatic AE. ⁴⁶ | Included as phase II/III trial completed and phase III trial ongoing. |
| Excluded | | |
| AT-1501 | Two publications retrieved. Both are conference abstracts presenting results of a phase I study. ^{47,48} | Excluded as phase II trial not completed |
| Engensis (VM202) | Three publications retrieved including 2 conference abstracts ^{49,50} and one full article reporting on an open-label study. ⁵¹ | Excluded as phase II trial not completed |
| Nicotinamide riboside and pterostilbene (EH301) | One publication of a single-centre pilot RCT. ⁵² | Excluded as only a pilot study completed. |
| CNM-Au8 | Two publications retrieved. A full-text article describing the RESCUE-ALS study protocol and an abstract with preliminary results. ^{53,54} | Excluded as phase II trial data not provided in the retrieved abstract. |
| HEALEY ALS Platform Trial (4 arms): <ul style="list-style-type: none"> • Zilucoplan • Verdiperstat • CNM-Au8 • Pridopidine | No publications retrieved. | Excluded as phase II trial not completed for these drugs. |

AE = adverse event; ALS = amyotrophic lateral sclerosis; PD = pharmacodynamics; RCT = randomized clinical trial.

of decline of the ALSFRS-R score and survival time. Safety was assessed throughout the trial. Ten patients were enrolled; 9 completed the treatment. There were no treatment-related severe adverse events (AEs) during the 6-month follow-up period. Compared with 18 matched (historical) controls, there was no difference ($P = 0.263$) in the decline of the ALSFRS-R score in the fasudil group during the first 3 months; the decline was greater in the fasudil group during the second 3 months ($P = 0.008$). There was no between-group difference in the survival time observed during the 6-month follow-up period (no P value reported).³⁰

The second study (ROCK-ALS; NCT03792490) is an ongoing phase IIa, multi-centre, randomized, double-blind, placebo-controlled trial assessing the safety, tolerability, and efficacy of fasudil administered IV in 2 different doses, 30 mg/day and 60 mg/day. It targets enrolling 120 patients (80 patients on fasudil and 40 patients on placebo); these patients will come from approximately 16 trial sites located in Germany, France, and Switzerland. The estimated study completion date is July 2022.¹⁶ Three case reports of the compassionate use of fasudil in patients with ALS were also recently published.³¹

Ibudilast (MN-166)

There are 2 relevant clinical trials for ibudilast. The first is a phase II single-centre, randomized, double-blind, placebo-controlled trial (IBU-ALS-1201; NCT02238626). Randomization followed a 2:1 ratio (ibudilast: placebo). The double-blind component lasted 6 months; it was followed by a 6-month open-label phase (for placebo patients only). The study evaluated the safety, tolerability, and clinical responsiveness of ibudilast, as add-on therapy in 60 patients with ALS. Ibudilast was administered at a daily dose of 60 mg; patients were also using riluzole (100 mg per day). The study was completed in December 2017; results were taken from the National Institute of Health (NIH) trial registry.¹⁸ Although it initially aimed at enrolling 60 patients, a total of 70 patients participated. Patients were divided into early ALS (ibudilast = 34; placebo = 17) and advanced ALS cohorts (ibudilast = 11; placebo $n = 8$). The primary outcome was safety, assessed by monitoring and recording all treatment emergent AEs (TEAEs), including serious AEs and discontinuations due to treatment emergent AEs that occurred over 6 months. All patients in each group reported AEs.¹⁸ Serious AEs were reported as follows:

- Early ALS cohort: placebo = 1 of 17 (5.9%); ibudilast = 5 of 34 (14.7%)
- Advanced ALS cohort: placebo = 2 of 8 (25.0%); ibudilast = 3 of 11 (27.3%).¹⁸

There were several secondary outcomes measured over the 6-month observation period of the trial. Results of key secondary outcomes are presented below (no P value reported).¹⁸

- Mean change in ALSFRS-R total score from baseline to month 6 (mean, standard deviation [SD])
 - Early ALS cohort: placebo = -3.8 (3.9); ibudilast = -4.5 (5.1)
 - Advanced ALS cohort: placebo = -2.2 (2.6); ibudilast = -4.8 (4.9).¹⁸
- Change in respiratory function (breathing capacity) from baseline to month 6, as measured by slow vital capacity (mean, SD):
 - Early ALS cohort: placebo = -6.1 (9.3); ibudilast = -10.1 (9.9)
 - Advanced ALS cohort: placebo = -12.2 (7.1); ibudilast = -11.1 (18.7).¹⁸
- Muscle strength measured by manual muscle testing and instrumented hand-held dynamometry (mean, SD):
 - Early ALS cohort: placebo = -3.9 (5.4); ibudilast = -4.9 (5.5)

- Advanced ALS cohort: placebo = -1.3 (2.4); ibudilast = -4.4 (3.6).¹⁸
- Change in quality of life as measured by the Amyotrophic Lateral Sclerosis Assessment Questionnaire – 5 (mean, SD):
 - Early ALS cohort: placebo = 2.1 (3.0); ibudilast = 1.6 (2.8)
 - Advanced ALS cohort: placebo = -0.7 (2.1); ibudilast = 4.8 (3.6).¹⁸
- Clinical Global Impression of Change (mean, SD):
 - Early ALS cohort: placebo = -1.0 (0.8); ibudilast = -1.4 (0.8)
 - Advanced ALS cohort: placebo = -1.3 (0.5); ibudilast = -1.6 (0.7).¹⁸

The second study of interest is an ongoing phase IIb/III multi-centre, randomized, double-blind, placebo-controlled, parallel-group clinical trial (COMBAT-ALS, NCT04057898). This study aims to evaluate the efficacy, safety, and tolerability of ibudilast administered at a daily dose of 100 mg during 12 months to patients with ALS. This study part will be followed by a 6-month, open-label, extension phase. The estimated completion date of this trial is December 2024.⁵⁶

Inosine

A multi-centre phase II trial was conducted (SURE-ALS2, NCT03168711).⁵⁷ This randomized, placebo-controlled trial was completed in January 2020; results are not published but are available on the NIH trial registry.⁵⁷ The primary objective of the SURE-ALS2 study was to determine the safety and tolerability of daily orally administered inosine. Dosing was selected to moderately elevate serum urate levels over 20 weeks. The primary end points were the number of participants with AEs and tolerability which was defined as the number of participants able to complete the 20-week study without permanently discontinuing the study drug or suspending the study drug for greater than 28 days. Adult patients (ages 18 to 85) were recruited from 3 US ALS centres. Key inclusion criteria included sALS or fALS diagnosed as possible, laboratory-supported probable, probable, or definite disease as defined by revised El Escorial criteria, slow vital capacity $\geq 60\%$ at the screening visit, and serum urate < 5.5 mg/dL at screening (i.e., below the population median serum urate levels). The study aimed at enrolling 48 patients but only 23 initiated treatments, 14 patients in the inosine group and 9 patients in the placebo group. Of these, 19 completed the study, 12 patients in the inosine group and 7 patients in the control group.⁵⁷ Results reported are as follows (no P value reported):

- All-cause mortality: inosine: 0 of 14 (0.0%); placebo: 1 of 9 (11.1%)
- Serious AEs: inosine: 4 of 14 (28.6%); placebo: 1 of 9 (11.1%)
- Other AEs: inosine: 11 of 14 (78.6%); placebo: 7 of 9 (77.8%).⁵⁷

Masitinib (AB1010)

There are 2 registered clinical trials for this emerging drug. The first 1 is a phase II/III, multi-centre, randomized, double-blind, placebo-controlled, parallel-group, trial that assessed the efficacy and safety of masitinib in patients with ALS (NCT02588677; AB10015). Two different dosing regimens of masitinib were studied, 3 mg/kg/day and 4.5 mg/kg/day; all patients also received riluzole. The study was completed in March 2018.⁵⁸ Results and subgroup analyses related to study AB10015 were presented in 4 conference abstracts in 2017 and 2018,^{40,42-44} in a publication in 2019,⁹ and in a recent published long-term survival analysis.²³

In the AB10015 study, eligible patients were adults aged 18 to 75 years with a diagnosis based on revised El Escorial criteria of laboratory-supported probable, probable, or definite ALS, disease duration less than 36 months duration, and FVC of at least 60% at baseline.⁹ Patients were categorized according to the ALSFRS-R progression rate, calculated from disease onset to baseline with a dichotomizing cut-off at 1.1 points per month. Those with a post-onset ALSFRS-R progression rate of less than 1.1 points per month were categorized as normal progressors; they represent an estimated 84% of the ALS population. The other enrolled patients were fast progressors. It was predetermined that patients categorized as normal progressors receiving masitinib 4.5 mg/kg daily were predefined as the primary efficacy population. The primary end point was the decline from baseline of ALSFRS-R total score at week-48. Secondary end points included: time-to-event analysis (an end point driven by both death and a fixed disease progression on the ALSFRS-R score, defined here as a deterioration of 9 points from baseline or death), combined assessment of function and survival, change from baseline in the ALAQ-40 (ALS Assessment Questionnaire 40-item4) score (ALAQ-40 being an ALS quality of life patient questionnaire), FVC; limb muscle strength using hand-held dynamometry; and overall survival.⁹ Predefined secondary analyses included assessment of the broader normal and fast progressors masitinib 4.5 mg/kg daily cohort and low-dose (masitinib 3.0 mg/kg daily) cohorts. Safety monitoring was pursued until day 28 following discontinuation of the study drug. A total of 394 patients were randomized from 34 sites located in 9 countries: 133 patients received placebo, 131 patients received masitinib 3.0 mg/kg daily, and 130 patients received masitinib 4.5 mg/kg daily. The primary efficacy population (i.e., normal progressors receiving masitinib 4.5 mg/kg daily versus placebo) comprised 105 and 113 patients, respectively.⁹ For the primary efficacy population, the between-group difference in decline from baseline of ALSFRS-R total score at week-48 was 3.39 (masitinib = -9.24; placebo = -12.63); 95% confidence interval (CI), 0.65 to 6.13, P = 0.016. This represented a 27% slowing of ALSFRS-R deterioration. There were no differences in the decline from baseline of ALSFRS-R total score at week 48 for the secondary analysis populations of the normal and fast progressor masitinib 4.5 mg per kg daily cohort or the low-dose (masitinib 3.0 mg/kg daily) cohort.⁹ With respect to the impact of masitinib on the secondary end points for the primary efficacy population of normal progressors receiving masitinib 4.5 mg/kg daily, a difference in favour of masitinib was observed, compared to placebo, for 3 of these end points, with:

- a lower deterioration in quality of life, as measured by the ALAQ-40 scale, with a between-group difference of 29% (change in least square mean from baseline of 19.42 for the masitinib versus 27.18 for the placebo group; P = 0.008)⁹
- a lower deterioration in respiratory function, as measured by FVC, with a between-group difference of 22% (change in least square mean from baseline of -26.45 for masitinib versus -33.99 for placebo; P = 0.03)⁹
- a delay of 25% in disease progression, as measured through the time-to-event analysis (20 months for masitinib versus 16 months for placebo, P = 0.016).⁹

There was no difference in overall survival in either the masitinib (4.5 mg/kg daily) or placebo groups. With respect to safety, the percentage of treatment-emergent AEs was 88% for masitinib 4.5 mg/kg daily, 85% for masitinib 3.0 mg/kg daily, and 79% for placebo. The percentage of serious AEs was 31%, 23%, and 18%, respectively. However, 1 isolated case (0.8%) of autoimmune-like hepatitis was reported in the masitinib 4.5 mg/kg daily group with the patient showing increased liver transaminase levels (grade 3) at week 24. This event resolved after masitinib was discontinued and a combination of prednisone and azathioprine was initiated. Three other cases of increased transaminases were reported (two patients on

masitinib 4.5 mg/kg daily and 1 patient on masitinib 3 mg/kg daily). All were non-severe and resolved without sequelae following temporary treatment interruption.⁹ Compared to placebo, the addition of masitinib – administered orally at a dose of 4.5 mg/kg daily – to riluzole (100 mg daily) slowed the decline in the ALSFRS-R score of patients pertaining to the study's predefined primary efficacy population.

The second study is a phase III, multi-centre, double-blind, randomized, placebo-controlled, parallel-group, trial of oral masitinib in the treatment of patients with ALS (NCT03127267; AB19001). Two ascending dose titrations of masitinib are evaluated in this study, 3.0 mg per kg daily with a dose escalation to 4.5 mg per kg daily after 4 weeks and 3.0 mg per kg daily with a dose escalation to 4.5 mg per kg daily after 4 weeks followed by another dose escalation to 6.0 mg/kg/day after 4 more weeks of treatment. All patients are also receiving riluzole 50 mg twice daily. This study is still recruiting patients and is targeted for completion in December 2022.²⁴ The objective of the AB19001 study is to confirm findings from study AB10015, while using a dosing regimen designed to optimize the benefit-risk balance of masitinib.⁴¹ The primary and secondary end points are the same as those of study AB19005.^{24,41}

Concurrent Developments

Several drugs are also in earlier clinical development for the treatment of patients of ALS. Although describing all potential drug candidates for the treatment of ALS is beyond the scope of this report, several other new or repurposed drugs were identified during this review. They are briefly described in Appendix 1 Tables 4, 5, and 6. Clinical trial information related to these drugs is summarized in Appendix 1 Tables 7, 8, and 9.

Considerations for Future Uptake

Given there are currently only 2 drugs approved in Canada for the treatment of patients with ALS, the number of emerging drugs in the research pipeline for this condition is encouraging. However, as many of these drugs still must complete their phase II and III clinical development, there is considerable uncertainty as to when they will become available to clinicians and patients. Nonetheless, it is possible to identify 2 key potential implementation considerations. The first 1 concerns the indication of certain drugs with respect to the subtype of ALS they will be intended for. Among the discussed drugs, prescribing antisense drug ION363 (jacifusen) would be expected to be limited to patients with fused in sarcoma (FUS)-ALS, a rare genetic form of ALS caused by mutations in the FUS gene. Also, prescribing masitinib may be limited to ALS patients categorized as normal progressors; that is, those with ALSFRS-R progression rate from disease onset to baseline of less than 1.1 points per month.⁹ This means that additional investigations may be required to characterize potential patient candidates for these drugs to ensure optimal patient selection for these therapies. In addition, should these drugs be eventually reimbursed by publicly funded drug plans, clear reimbursement criteria will need to be developed.

The second implementation consideration is the route of administration, and in some cases, the dosing schedule. Most considerations will not really be an issue for the several orally administered emerging drugs, although availability of a liquid form, in addition to the oral solid form, may be desirable for patients who develop swallowing difficulties. However, these considerations will be an issue for emerging drugs that require parenteral administration as additional support will be required. Drug administration issues may be more easily resolved for some parenteral drugs than others. For example it could be thought that a self-administration program could be developed by the manufacturer of zilucoplan as this drug requires subcutaneous administration.⁵⁹ Such program would also need to be adapted for caregivers of patients with more severe ALS as these patients may not be able to self-inject the medication. However, homecare services may be needed for patients to whom clinicians would prescribe drugs requiring IV administration; examples of such IV drugs include AT-1501,⁶⁰ fasudil,¹⁶ and SLS-005.⁶¹ This may also be the case for drugs with more complex dosing schemes such as engensis (VM202) which, based on current state of research, requires multiple intramuscular injections administered on bilateral upper and lower limbs on alternative weeks.⁵¹ Hospital services may also be required for 2 drugs that require intrathecal administration: tofersen⁶² and ION 363.⁶³ Of note, intrathecal administration involves the direct injection of the drug into the cerebrospinal fluid within the intrathecal space of the spinal column. It is a specialized way of administering drugs that requires appropriately trained hospital personnel.⁶⁴ Consequently, it may be expected that specialized programs would need to be developed to support administration of these drugs.

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Appendix 1: Concurrent Developments

Note that this appendix has not been copy-edited.

There are several drugs currently approved in Canada for non-ALS indications and that are being investigated for the treatment of ALS (Table 4).

Table 4: Repurposed Drugs – Description of Drugs Marketed in Canada for non-ALS Indications Under Evaluation for ALS

| Drug | Approved use in Canada | Drug class or mechanism of action | Administration |
|---|--|--|----------------|
| Bosutinib ⁶⁵ | Treatment of adults with Philadelphia chromosome positive chronic myelogenous leukemia | Protein-tyrosine kinase inhibitor | Oral |
| Colchicine ^{66,67} | Prophylaxis and treatment of gout flares in adults | Enhances the expression of HSP B8 which recognizes and promotes the autophagy-mediated removal of misfolded mutant SOD1 and TDP-43 fragments from ALS motor neurons. Colchicine also enhances several autophagy players while blocking TDP-43 accumulation in neurons. | Oral |
| Cromolyn ^{68,69,70,71} | Treatment of asthma and the prevention of the signs and symptoms of seasonal allergic conjunctivitis | Cromolyn alters inflammatory response. | Inhalation |
| Fingolimod ^{72,73} | Treatment of relapsing-remitting form of multiple sclerosis | Fingolimod blocks signaling from the sphingosine 1-phosphate receptor, trapping the immune cells in the lymph nodes and therefore preventing them from reaching the nervous system to cause inflammation. By reducing inflammation, it is thought that fingolimod will slow the progression of ALS. | Oral |
| Lithium combined with valproic acid ^{74,75,76} | Treatment of manic episodes of manic-depressive illness and epileptic seizures | Lithium directly inhibits GSK-3 while valproic acid inhibits this kinase indirectly. GSK-3 is involved in numerous biological pathways including cancer, inflammation and neurodegenerative diseases. In ALS, an up-regulation of GSK-3 in spinal cord and frontal and temporal cortex has been described. GSK-3 is also expressed in peripheral blood mononuclear cells of patients with ALS and these levels of active kinase are directly related to clinical symptoms. | Oral |

| Drug | Approved use in Canada | Drug class or mechanism of action | Administration |
|--|---|---|----------------|
| Nicotinamide riboside and pterostilbene (EH301) ⁷⁷⁻⁷⁹ | Dietary supplements | It is thought that increasing activity in sirtuins, along with increased access to NAD, can delay disease progression. Nicotinamide riboside can increase cells' access to NAD and pterostilben may stimulate sirtuins. Note: Table 2 provides further information. | Oral |
| Rapamycin (sirolimus) ^{76,80} | Prophylaxis of organ rejection in patients receiving allogeneic renal transplants | Rapamycin acts on the mTOR enzyme, an enzyme part of the protein kinases family. mTOR has two functionally different protein complexes, mTORC1 and mTORC2. Rapamycin targets mTORC1 selectively as an allosteric inhibitor, modulating mechanisms that play an important role in ALS, including autophagy and neuro-inflammation. | Oral |

ALS = amyotrophic lateral sclerosis; GSK = glycogen synthase kinase; HSP = heat shock protein; mTOR = the mammalian target of rapamycin; NAD = nicotinamide adenine dinucleotide; SOD1 = superoxide dismutase 1.

Table 5 describes select new molecular entities in early development phases I or II for the treatment of patients with ALS.

Table 5: Description of Emerging Drugs in Early Clinical Development

| Drug | Drug class or mechanism of action | Administration |
|------------------------------------|--|----------------|
| AT-1501 ^{81,60} | Monoclonal antibody against CD40L. It is anticipated that inhibition of CD40L could block or delay the activation of the damaging inflammatory immune response. This could delay ALS onset or slow its progression. Note: Table 2 provides further information. | IV |
| DNL343 ^{82,83} | Small molecule designed to activate eIF2B. With cellular stress, the production of eIF2B is suppressed leading to the formation of toxic protein granules. These stress granules are thought to be precursors of TDP-43 aggregates; these aggregates are frequently encountered in ALS. Activating eIF2B is expected to clear TDP-43 aggregates and improve the survival of nerve cells. | Oral |
| DNL788 (SAR443820) ⁸² | DNL 788 is a RIPK1 inhibitor. Increased activity of RIPK1 causes inflammation and cell death in the brain. It also contributes to neurodegeneration in conditions such as ALS. | Oral |
| Engensis (VM202) ^{81,84} | Engensis is an HGF gene therapy. By increasing the production of HGF, engensis is expected to delay or stop ALS progression. The drug is injected directly into selected muscles to regenerate both damaged motor neurons and muscles. Note: Table 2 provides further information. | IM |
| GDC-0134 (RG6000) ^{76,85} | GDC-0134 inhibits DLK, a kinase highly expressed in neuronal cells. DLK plays a key role in the progressive neurodegeneration that occurs in neurological diseases such as ALS. | Oral |

| Drug | Drug class or mechanism of action | Administration |
|---|---|---|
| <p>HEALEY ALS Platform Trial (4 arms)^{11,21,59}:</p> <ul style="list-style-type: none"> • Zilucoplan⁵⁹ • Verdiperstat⁵⁹ • CNM-Au8⁵⁹ • Pridopidine^{11,81} | <p>The HEALEY ALS Platform Trial is a trial model designed to accelerate the development of ALS therapies by assessing multiple treatment candidates simultaneously and sharing placebo groups. It began enrolling patients in July 2020; new investigational drugs will join the Platform as they become available.</p> <ul style="list-style-type: none"> • Zilucoplan is a C5 protein blocker. The C5 protein plays a role in the complement system, a part of the immune system abnormally activated in ALS. • Verdiperstat selectively blocks the myeloperoxidase enzyme, an enzyme involved in oxidative stress and inflammation in the brain and spinal cord. • CNM-Au8 is composed of gold nanocrystals designed to provide neuroprotective effect by improving nerve cells' survival, function, and communication. • Pridopidine is a sigma-1 receptor agonist. Decrease in or loss of function in the sigma-1 receptor may result in the development of ALS. <p>Note: Table 2 provides further information.</p> | <p>SC</p> <p>Oral</p> <p>Oral (liquid suspension)</p> <p>Oral</p> |
| <p>ION363 (jacifusen)^{86,87,10,63}</p> | <p>Antisense drug designed to reduce the production of the FUS protein. Mutation of the FUS gene causes a rare genetic form of ALS. FUS-ALS is the third most common genetic cause of ALS and has a higher incidence in juvenile ALS. It however only accounts for 4% of all familial motor neurone disease.</p> | <p>IT</p> |
| <p>SLS-005 (trehalose)⁶¹</p> | <p>SLS-005 is a natural autophagy-promoting sugar molecule found in plants, fungi, and bacteria. In pre-clinical studies, it promoted the clearance of ALS-associated TDP-43 and SOD1 proteins, thus showing the potential to delay ALS progression and preserve motor neurons.</p> | <p>IV</p> |

ALS = amyotrophic lateral sclerosis; CD40L = CD40 ligand; DLK = dual leucine zipper kinase; eIF2B = eukaryotic translation initiation factor 2B; FUS = Fused in Sarcoma; HGF = hepatocyte growth factor; IM = intramuscular injection; IT = intrathecal injection; IV = intravenous injection; RIPK1 = receptor-interacting Ser/Thr protein kinase 1; S/C: subcutaneous injection.

There are also other drug candidates for ALS that have progressed to a relatively advanced clinical development stage. However, their future may be considered uncertain mainly because some studies have not met their key endpoints (Table 6).

Table 6: Description of Emerging Drugs in Late Clinical Development with Uncertain Future

| Drug | Drug class or mechanism of action | Administration |
|-------------------------------------|--|----------------|
| Arimoclomol ⁸⁸ | Arimoclomol increases the production of HSPs; these are proteins involved in stress response. One of those HSPs binds SOD1, a malfunctioning protein in ALS patients carrying mutations in the SOD1 gene. Malfunctioning SOD1 may accumulate in neurons and cause them to die. | Oral |
| Ravulizumab ^{89,90} | Ravulizumab is a long-acting C5 complement inhibitor. Under certain circumstances, the C5 protein is involved in the over-response of the body' immune system. Note: In Canada, ravulizumab is approved, under tradename Ultomiris, for the treatment of adults with paroxysmal nocturnal hemoglobinuria. | IV |
| Reldesemtiv ^{91,92} | Reldesemtiv is a next-generation fast skeletal muscle troponin activator. | Oral |
| Tofersen (BIIB067) ^{93,62} | Tofersen is an antisense oligonucleotide that mediates the degradation of SOD1 messenger RNA to reduce SOD1 protein synthesis. | IT |

ALS = amyotrophic lateral sclerosis; C5 = complement component 5; HSP = heat shock protein; SOD1 = superoxide dismutase 1; IT = intrathecal

Table 7: Research Status of Repurposed Drugs for ALS

| Drug | Study name and National Clinical Trial number | Design and study completion date | Study objective | Primary end point | Findings |
|---|---|---|---|---|---|
| Bosutinib ⁹⁴ | iDReAM NCT04744532 | Phase I, multi-centre, open-label, dose-escalation trial (Japan) N = 24 March 2022 | To evaluate the safety and tolerability of bosutinib to determine the maximum tolerated dose and a recommended phase II dose. | Dose-limiting toxicity | NA |
| Colchicine ⁶⁷ | Co-ALS NCT03693781 | Phase II (Italy) N = 54 January 2022 | To evaluate the effects of two different doses of colchicine (0.01 mg/kg/day or 0.005 mg/kg/day), compared to placebo. | Disease progression as defined by changes in the ALSFRS-R score | NA |
| Cromolyn ⁷⁰ | NCT04428775 | Phase IIa, multi-centre randomized, open-label, multi-dose trial N = 12 October 2021 | Determine whether cromolyn, administered by inhalation through dry powder inhaler over 12 weeks, positively impacted neuro-inflammatory biomarkers and slowed functional decline in patients with mild to moderate ALS. | Plasma neuro-inflammatory biomarkers. | NA |
| Fingolimod ^{73,95} | NCT01786174 | Phase IIa randomized, double-blind, placebo-controlled trial N = 30 May 2015 | To determine the acute safety and tolerability of oral administration of fingolimod 0.5 mg daily compared to a matched oral placebo administered daily. | Safety and tolerability | The trial met its primary end point, and results suggest that the treatment was well tolerated in ALS patients. No serious AEs were reported. |
| Lithium combined with valproic acid ⁹⁶ | NCT03204500 | Phase II, randomized, double-blind, placebo-controlled pilot trial N = 43 August 2019 | To evaluate the effect of dual lithium and valproic acid therapy on progression of ALS. | Progression of ALS measured as changes from baseline in ALSFRS-R. | NA |

| Drug | Study name and National Clinical Trial number | Design and study completion date | Study objective | Primary end point | Findings |
|--|---|--|--|---|--|
| Nicotinamide riboside and pterostilbene (EH301) ^{52,97,98,79} | NCT03489200 | Randomized placebo-controlled pilot trial N = 32 June 2017 | To evaluate the efficacy and tolerability of EH301 in patients with ALS. | ALSFRS-R score | <ul style="list-style-type: none"> • Placebo: decline at 2 (- 3.0) and 4 (-5.5) months • EH301: improvement at 2 (3.4) and 4 (2.5) months), p < 0.01. |
| | NO-ALS NCT04562831 | Randomized placebo-controlled trial N = 380 October 2022 | To determine whether combination therapy with EH301 can inhibit neurodegeneration in ALS and thereby delay disease development, increase survival and improve the quality of life of patients with ALS. | Disease progression as assessed by ALSFRS-R | NA |
| | NO-ALS Extension Study NCT05095571 | Single group multi-centre open-label trial as a follow-up of the NO-ALS trial. N = 300 October 2023 | To evaluate AEs, give patients the possibility of compassionate use of EH301 and determine if EH301 will decrease progression of motor symptoms and loss of vital capacity, as well as increase survival time, in patients with ALS. | Incidence of AEs during study (12 months). | NA |
| Rapamycin (Sirolimus) ^{76,99} | RAP-ALS NCT03359538 | Phase II multi-centre, randomized, double-blind trial (Italy). N = 63 September 2021 (active but no longer recruiting) | To study the biological response of rapamycin, administered in two different doses, in ALS patients to obtain predictive information for a larger study. | Proportion of patients exhibiting a positive response to the treatment. | NA |

ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; N/A = not available; RCT = randomized clinical trial.

Table 8: Research Status of Emerging Drugs in Early Clinical Development

| Drug | Study name and National Clinical Trial number | Design and study completion date | Study objective | Primary end point | Findings |
|------------------------------|---|---|--|--|---|
| AT-1501 ^{47,48,100} | Phase I: N/A | Placebo-controlled, sequential, dose-escalation trial N = 28 healthy individuals and 4 adults with ALS. 2021 (estimated based on conference abstracts). | To determine the safety, PK, and functional activity of AT-1501. | Safety and tolerability of AT-1501. | AT-1501 was well tolerated in all study participants. Proportion of patients with at least one TEAE: • AT-1501: 54% • Placebo: 62% The frequency of these AEs ranged from 33% to 66.7% across the groups and did not appear to be dose related. |
| | Phase IIa: NCT04322149 | Multi-centre, open-label, multiple doses trial. N = 54 March 2022 | To evaluate the safety and tolerability of multiple doses of AT-1501 in adults with ALS. | Safety and tolerability of AT-1501, measured as incidence of AEs observed over a period of about 5 months. | NA |

| Drug | Study name and National Clinical Trial number | Design and study completion date | Study objective | Primary end point | Findings |
|------------------------------|---|---|---|--|---|
| DNL343 ^{101-103,83} | Phase I: NCT04268784 | Single-centre, randomized, double-blind, placebo-controlled trial N = 88 August 2021 | To evaluate the safety, tolerability, PK, and PD of DNL343 In healthy volunteers. | Incidence and severity of TEAEs + PK parameters: AUC, Cmax, Tmax, λz with the respective t½. | The sponsor announced in October 2021 that DNL343 had achieved safety and biomarker goals of the study. The drug was well tolerated for up to 14 days and the PK profile supported dosing once a day. |
| | Phase Ib: NCT05006352 | Multicenter, randomized, placebo-controlled, double-blind study followed by an open-label extension. N = 30 December 2023 | To determine the safety, PK, and PD of DNL343 in patients with ALS. | Incidence of TEAEs + PK parameters: AUC, Cmax, Ctough, Tmax and CSF-to-plasma concentration ratio. | NA |

| Drug | Study name and National Clinical Trial number | Design and study completion date | Study objective | Primary end point | Findings |
|---|---|---|---|--|---|
| DNL788 (SAR443820) ^{82,83,101,104} | Phase I: NCT04982991 | Open-label, 3-treatment period, 1-sequence, crossover trial N = 14 October 2021 | To assess the PK, safety and tolerability of single ascending oral doses of SAR443820 in healthy adult Chinese and Japanese female and male patients. | Cmax, AUC, AEs. | The sponsor announced in October 2021 positive PK and safety results. Also SAR443820 received fast-track designation from the FDA. |
| | HIMALAYA | Multi-centre, randomized, double-blind, placebo-controlled trial with open-label long-term extension. N = N/A Study to be initiated early 2022. | To evaluate the efficacy and safety of DNL788 in adults with ALS. | NA | NA |
| Engensis (VM202) ^{51,105,106} | Phase I/II: NCT02039401 | Open-label study N = 18 December 2017 | To determine the safety and tolerability of IM injections of VM202 at different injection sites in people with ALS. | Number of participants with serious and non-serious AEs. | 79 AEs in 17 patients (94.4%), including 26 injection site reactions. AEs were mild or moderate (bruising, soreness, erythema, pain). |
| | Phase IIa: REVivals-1A NCT04632225 | Multi-centre, randomized, double-blind, placebo-controlled trial. N = 18 May 2022 | to evaluate the safety of IM administration of engensis in participants with ALS as compared to placebo. | incidence of TEAEs after injections, injection site reactions, and clinically significant laboratory values. | NA |

| Drug | Study name and National Clinical Trial number | Design and study completion date | Study objective | Primary end point | Findings |
|-------------------------------------|---|---|---|--|----------|
| GDC-0134 (RG6000) ^{85,107} | Phase I: NCT02655614 | Multi-centre, double-blind, placebo-controlled, single- and multiple-ascending-dose trial with open-label safety expansion. N = 54 March 2020 | To determine the safety, tolerability, and PK properties of orally administered GDC-0134 in patients with ALS. | Percentage of patients with AEs, clinically significant abnormalities in laboratory, vital signs, ECG, or physical examination findings. | NA |
| CNM-Au8 ^{53,54,108,109} | Phase II: RESCUE-ALS NCT04098406 | Multi-centre, randomized, double-blind, parallel-group, placebo-controlled trial N = 42 August 2022 | to assess CNM-Au8 as a disease-modifying agent for the treatment of ALS by utilizing electrophysiological measures to detect preservation of motor neuron function. | the mean change in motor unit number index measured by electromyography. | NA |
| | Phase II: REPAIR-ALS NCT03843710 | Open-label, investigator blinded, sequential cohort N = 24 July 2022 | to assess the central nervous system metabolic effects, safety, pharmacokinetics, and pharmacodynamics of CNM-Au8 in patients diagnosed with ALS within 12 months of screening. | the ratio of the oxidized to reduced form of nicotinamide adenine dinucleotide measured non-invasively by ³¹ P magnetic resonance spectroscopy. | NA |

| Drug | Study name and National Clinical Trial number | Design and study completion date | Study objective | Primary end point | Findings |
|--|--|--|---|---|----------|
| HEALEY ALS Platform Trial ¹¹⁰ | phase II or III studies NCT04297683 5 regimens being studied: <ul style="list-style-type: none"> • Regimen A: Zilucoplan¹¹¹ • Regimen B: Verdiperstat¹¹² • Regimen C: CNM-Au8^{113*} • Regimen D: Pridopidine¹¹⁴ • Regimen E: SLS-005 (trehalose)^{61,115} | Perpetual multi-centre, multi-regimen trial N = 640 November 2022 | to evaluate the safety and efficacy of investigational products for the treatment of ALS. Each investigational product will be tested in a regimen. | change in disease severity over time as measured by ALSFRS-R. | NA |
| Regimen A: Zilucoplan ¹¹¹ | Phase II/III NCT04436497 | Multi-centre randomized placebo-controlled clinical trial N = 162 June 2023 | To evaluate the safety and efficacy of S/C zilucoplan in patients with ALS. | Change in disease severity over time as measured by ALSFRS-R. | NA |
| Regimen B: Verdiperstat ¹¹² | Phase II/III NCT04436510 | Multi-centre randomized placebo-controlled clinical trial N = 167 April 2023 | To evaluate the safety and efficacy of oral verdiperstat in patients with ALS. | Change in disease severity over time as measured by ALSFRS-R. | NA |
| Regimen C: CNM-Au8 ^{113a} | phase II/III NCT04414345 | multi-centre randomized placebo-controlled clinical trial N = 161 April 2023 | To evaluate the safety and efficacy of oral CNM-Au8 in patients with ALS. | change in disease severity over time as measured by ALSFRS-R. | NA |

| Drug | Study name and National Clinical Trial number | Design and study completion date | Study objective | Primary end point | Findings |
|--|--|---|--|---|----------|
| Regimen D: Pridopidine ¹¹⁴ | Phase II/III NCT04615923 | Multi-centre randomized placebo-controlled trial N = 160 September 2022 | To evaluate the safety and efficacy of oral pridopidine in patients with ALS. | Change in disease severity over time as measured by ALSFRS-R. | NA |
| Regimen E: SLS-005 (trehalose) ^{61,115} | Phase IIb/III trial NCT05136885 SLS-005 was recently granted the orphan drug designation by the FDA and EMA. | Multi-centre randomized placebo-controlled trial N = 160 October 2023 | To evaluate the safety and efficacy of SLS-005 (trehalose injection, 90.5 mg/mL for IV infusion) in patients with ALS. | Change in disease severity over time as measured by ALSFRS-R. | NA |
| ION363 (jacifusen) ^{10,63} | Phase I to III NCT04768972 Note: The pivotal study is building from the sponsor's expanded access program. | Multi-centre, two-part trial. Part 1: patients randomized in a 2:1 ratio to receive a multi-dose regimen of ION363 or placebo. Part 2: open-label component for all study patients. N = 64 March 2024 | To evaluate the efficacy, safety, PK and PD of IT administered ION363 in patients with FUS-ALS. | Functional impairment to be measured by joint rank analysis of the combined assessment of in-clinic ALSFRS-R total score, time of rescue or discontinuation from Part 1 and entering Part 2 due to a deterioration in function, and VAFS. | NA |

AE = adverse event; ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; AUC = area under the concentration-time curve; CSF = cerebrospinal fluid; C_{max} = maximum observed concentration; C_{trough} = trough concentration; ECG = electrocardiogram; EMA = European Medicines Agency; FUS-ALS = ALS with Fused in Sarcoma mutations; IM = intramuscular; IT = intrathecal; NA = not available; PD = pharmacodynamics; PK = pharmacokinetics; S/C = subcutaneous injection; TEAE = treatment-emergent adverse event; T_{max} = time to maximum observed concentration; λ_z = apparent terminal elimination rate constant; t_{1/2} = half-life; VAFS = ventilation assistance-free survival.

Table 9: Research Status of Emerging Drugs in Late Clinical Development with Uncertain Future

| Drug | Status of clinical development program | Decision of the drug sponsor |
|--------------------------------------|--|---|
| Arimocloamol ^{88,116-118} | The development of arimocloamol had progressed to a phase III double-blind, placebo-controlled clinical trial of 245 patients with ALS (ORARIALS-01; NCT03491462). Arimocloamol had also earned the fast-track designation from the FDA for the treatment of ALS in May of 2020. However, one year later, the drug sponsor, Orphazyme, indicated that arimocloamol had failed to be more effective than placebo in the phase III study on either its primary end point (76-week CAFS score) or secondary endpoints (PAV, ALSFRS-R, SVC). | In May of 2021, Orphazyme indicated that they intend to use the knowledge acquired from the ORARIALS-01 trial to inform the development of their drug pipeline on HSPs. |
| Ravulizumab ⁸⁹ | Ravulizumab was being evaluated for the treatment of ALS in a phase III randomized, double-blind, placebo-controlled multi-centre global (90 sites across North America, Europe and Asia) trial (CHAMPION-ALS). The trial enrolled 382 adults with sALS or fALS who had disease onset within the prior 36 months and who did not require respiratory support. The primary end point was change in ALSFRS-R score. | On August 20, 2021, Alexion, the drug sponsor, announced it was discontinuing CHAMPION-ALS. This decision was based on the recommendation of the IDMC which, based on their review of data from a pre-specified interim analysis, recommended the trial be discontinued due to lack of efficacy. |
| Reldesemtiv ^{91,92,119,120} | In 2019, Cytokinetics Incorporated, the drug sponsor, announced that phase II trial FORTITUDE-ALS (NCT03160898) had failed to meet its primary end point (SVC, p = 0.11) and secondary endpoints (ALSFRS-R, p = 0.09; slope of the Muscle Strength Mega-Score, p = 0.31). However, supplemental analyses showed that patients on reldesemtiv declined less than those on placebo for SVC and ALSFRS-R, with larger differences emerging over time. At that time, the sponsor indicated that while this trial had failed to meet its endpoints, results were encouraging and further validated the potential of skeletal muscle activation in treating patients with ALS. | In August 2021, the sponsor launched COURAGE-ALS (NCT04944784), a phase III double-blind, randomized, placebo-controlled trial of reldesemtiv in patients with ALS. The primary end point is ALSFRS-R total score. This study aims to randomize 555 patients to either reldesemtiv or placebo for 24 weeks. All patients will then receive reldesemtiv for another 24 weeks. The projected completion date is March 2024. |

| Drug | Status of clinical development program | Decision of the drug sponsor |
|--|--|---|
| Tofersen (BIIB067) ^{93,121,122} | <p>VALOR (NCT02623699) was 3-part study (phase I/II/III) to examine the efficacy, safety, tolerability, PK, and PD of tofersen (Part A was the SAD component, Part B the MAD component and Part C the fixed dose component; the latter part was in patients with ALS and confirmed SOD1 mutation). The study ended on July 15, 2021. In total, the study enrolled 178 participants, of which 108 participated in Part C (phase III). Topline results for Part C indicate the trial missed its primary end point (ALSFERS-R score from baseline to 28 weeks):</p> <ul style="list-style-type: none"> • Faster-progressing ALS patients: placebo: - 8.14; tofersen: - 6.98; difference: 1.2 (p = 0.97) • Slower-progressing ALS patients: placebo: - 2.73; tofersen: - 1.33; difference: 1.4 (no p value). <p>However, the use of tofersen was linked to changes in SOD1 and neurofilament light chain, a potential marker of neuronal degeneration.</p> | Biogen, the manufacturer of tofersen, has recently engaged in discussion with regulatory agencies to determine whether approval could be granted based on the available data. |

ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; CAFS = Combined Assessment of Function and Survival; fALS = familial ALS; HSP = heat shock protein; IDMC = Independent Data Monitoring Committee; MAD = multiple-ascending-dose; PAV = permanent assisted ventilation; PD = pharmacodynamics; PK = pharmacokinetics; SAD = single ascending dose; sALS = sporadic ALS; SVC = slow vital capacity.