

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

(also known as Lou Gehrig's Disease)

DISEASE FACT SHEET AND OPPORTUNITY FOR *TIRASEMTIV*

What is ALS?

ALS is a neurodegenerative disease that can attack both upper and lower motor neurons and causes degeneration throughout the brain and spinal cord. In patients with ALS, this progressive degeneration eventually leads to the death of the motor neurons. As these motor neurons die, the brain loses the ability to initiate and control muscle movement. With voluntary muscle action progressively affected, patients in the later stages of the disease may become totally paralyzed.¹

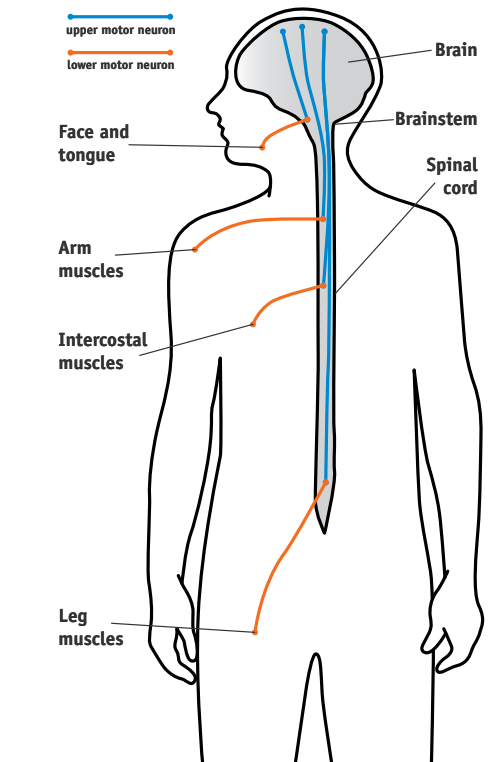
How common is ALS?

ALS affects as many as 30,000 Americans, with an estimated 5,600 new cases diagnosed each year in the U.S.^{1,2} ALS is 20% more common in men than women, however, with increasing age, the prevalence becomes more equal between men and women. The life expectancy of an ALS patient is 2-5 years from the time of diagnosis with 90-95% of those diagnosed with ALS having the sporadic form (SALS). Of the remaining ALS patient population, 5-10% have a family history of the disease (familial ALS, FALS). In cases of familial ALS, there is a 50% chance each offspring will develop the disease.¹

What are the symptoms of ALS?

The onset of ALS may be so subtle that the symptoms are often overlooked. The earliest symptoms may include twitching, cramping or stiffness of muscles; muscle weakness affecting an arm or a leg; slurred and nasal speech; or difficulty chewing or swallowing. These general complaints can then develop into more obvious weaknesses or atrophies that may cause a physician to suspect ALS.²

The parts of the body affected by the early symptoms of ALS depend on which motor neurons are damaged or lost first. In some cases, symptoms initially affect one of the legs and the patients may experience awkwardness when walking or running. Some patients first experience the effects of the disease in a hand or arm as difficulty increases with simple tasks requiring manual dexterity such as buttoning a shirt, writing, or turning a key in a lock. Other patients notice speech problems.²



Classic ALS (Upper & Lower Motor Neuron)^{4, 5}

- ~80% of motor neuron disease patients
- Upper motor neuron involvement in 3 of 4 regions of the CNS (brainstem or bulbar, cervical, thoracic, or lumbosacral spinal cord)
- The disease can progress over time from upper to lower motor neuron involvement or lower to upper motor neuron involvement
- This type of MND has the most rapid progression

Only Upper Motor Neuron^{4, 5}

- ~10% of motor neuron disease patients
- Also known as Primary Lateral Sclerosis or Progressive Bulbar Palsy
- Symptoms usually begin in one limb or in the mouth or throat and later spreading to other parts of the body
- Primary symptoms: stiffness, slowness, and clumsiness of movement
- Disease progression is slower than Classic ALS

Only Lower Motor Neuron^{4, 5}

- ~10% of motor neuron disease patients
- Also known as Progressive Muscular Atrophy
- Primary symptom is weakness which usually begins in one hand, one foot, or the tongue
- Disease progression is slower than Classic ALS

Regardless of the part of the body first affected by the disease, muscle weakness and atrophy spread to other parts of the body as the disease progresses. Patients have increasing problems with moving, swallowing, speaking or forming words. Symptoms of upper motor neuron involvement include tight and stiff muscles and exaggerated reflexes including an overactive gag reflex. Symptoms of lower motor neuron degeneration include muscle weakness and atrophy, muscle cramps, and fleeting twitches of muscles that can be seen under the skin.²

How is ALS diagnosed?

No one test can provide a definitive diagnosis of ALS, although the presence of upper and lower motor neuron signs in a single limb is strongly suggestive.² ALS is a rule-out diagnosis based on a series of clinical examinations and diagnostics. Clinical diagnosis depends upon history, physical examination, and laboratory and radiographic evaluations that are both consistent with ALS while excluding other diseases that may mimic ALS.¹ Patients with ALS often demonstrate signs and symptoms of both upper and lower motor neuron damage that cannot be attributed to other causes.² The time to diagnosis is highly variable and depends on the severity of the initial symptoms and how aggressive the patient is in seeking a definitive diagnosis.

| Rate of Progression: | | | Site of Onset: | | |
|----------------------|--------------|------------------------------------|----------------|--------------|-------------------------|
| Rapid | 10% patients | Life expectancy – less than 1 year | Bulbar | 20% patients | speech/swallowing onset |
| Average | 80% patients | Life expectancy – 3-5 years | Arm | 40% patients | Unilateral onset |
| Slow | 10% patients | Life expectancy – up to 10+ years | Leg | 40% patients | Unilateral onset |
| | | | Respiratory | <1% | |

Because the onset of ALS may be subtle, it can take up to one year for a patient to see a generalist or primary care physician. Depending on the symptoms, the patient may see other specialists before seeing a neuromuscular specialist or neurologist. The average neurologist may only see one ALS patient per year and may therefore be uncomfortable making the definitive diagnosis, even if he or she suspects ALS. For that reason, patients are often referred to an ALS Center of Excellence (CoE) to see an ALS specialist for diagnosis and subsequent patient management. As the disease progresses, patients who are unable to travel to a CoE may be cared for by a local neurologist who coordinates with an ALS specialist.

How does ALS progress?

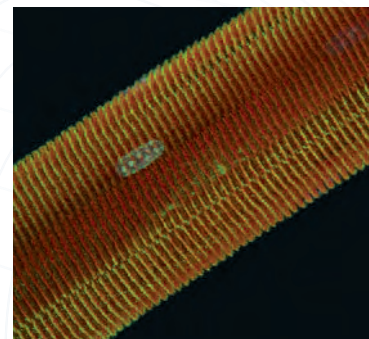
ALS begins in one region of the nervous system and causes the upper and lower motor neurons to die in that area; then the muscles they control become weaker and smaller. The strength of any voluntary muscle group can be affected in ALS, including those muscles that control facial expressions, chewing, swallowing, speaking, breathing and areas such as the neck, arms, trunk and legs. ALS can start in any muscle group and then move to any other; however, there is no predictable direction of where the weakness may spread next. The only exception is that when one arm or leg is involved first, then the opposite arm or leg is likely to weaken next.¹ Because of difficulty swallowing and chewing, maintaining weight can become a problem. In later stages of the disease, patients generally have difficulty breathing as the muscles of the respiratory system weaken. Patients eventually lose the ability to breathe on their own and must depend on support of a ventilator for survival. Patients also face an increased risk of pneumonia during later stages of ALS.²

How is ALS treated?

Currently there is no cure for ALS so effective symptomatic management and quality of life improvements are two of the primary goals in ALS patient care.¹

Approximately 50% of patients are treated at a CoE and, in the United States, there are 67 well-established CoEs for ALS care¹. At these CoEs, patients are seen as often as necessary (often every 3-6 months) by a treatment team and have access to a full range of specialists. This team consists of neuromuscular specialists, nurses, physical therapists/orthotists, occupational therapists, speech therapists, nutritionists, pulmonologists, gastroenterologists, and psychologists/social workers/psychiatrists.

To date, the Food and Drug Administration (FDA) has approved only one drug for the treatment of the disease – Rilutek® (riluzole). Rilutek® is believed to reduce damage to motor neurons by decreasing the release of glutamate³. Clinical trials with ALS patients demonstrated that Rilutek® provided an early increase in survival among the patients in whom treatment failed during the study (tracheostomy or death) by 60-90 days.³ The drug may also extend the time until which a patient needs ventilatory support³. Rilutek® does not reverse the damage already evident in motor neurons, and patients taking the drug must be monitored for liver damage and other possible side effects.² The vast majority of physicians will offer Rilutek® to all of their ALS patients. Some patients, however, choose not to take the drug for various reasons which may include the cost, and a perception that they are not receiving any benefit from the drug in terms of improved quality of life.



What R&D is Cytokinetics conducting to address ALS?

Tirasemtiv (formerly known as CK-2017357), a fast skeletal muscle troponin activator, is being developed as a potential treatment for diseases and conditions associated with aging, muscle wasting or neuromuscular dysfunction, such as ALS. *Tirasemtiv* selectively activates the fast skeletal muscle troponin complex and increases its sensitivity to calcium, resulting in increased skeletal muscle force and slowing of time to muscle fatigue.

Tirasemtiv, a novel skeletal muscle activator, is the lead drug candidate from Cytokinetics' skeletal muscle contractility program. *Tirasemtiv* selectively activates the fast skeletal muscle troponin complex by increasing its sensitivity to calcium and, in preclinical studies, demonstrated increases in skeletal muscle force in response to neuronal input and delays in the onset and reductions in the degree of muscle fatigue. *Tirasemtiv* was the subject of BENEFIT-ALS (**B**linded **E**valuation of **N**euromuscular **E**ffects and **F**unctional **I**mprovement with *Tirasemtiv* in **ALS**), a recently completed Phase IIb clinical trial. BENEFIT-ALS was a multi-national, double-blind, randomized, placebo-controlled, clinical trial designed to evaluate the safety, tolerability and efficacy of *tirasemtiv* in patients with amyotrophic lateral sclerosis (ALS). BENEFIT-ALS did not achieve its primary efficacy endpoint, the mean change from baseline in the ALS Functional Rating Scale in its revised form (ALSFRRS-R). Treatment with *tirasemtiv* resulted in a statistically significant and potentially clinically meaningful reduction in the decline of Slow Vital Capacity (SVC), a measure of the strength of the skeletal muscles responsible for breathing that has been shown to be an important predictor of disease progression and survival in prior trials of patients with ALS. The analyses of other pre-specified secondary efficacy endpoints produced mixed results. Results from BENEFIT-ALS were presented at the 66th Annual Meeting of the American Academy of Neurology on April 29, 2014 and at the Joint Congress of European Neurology on June 1, 2014. Cytokinetics expects to continue to analyze the data from BENEFIT-ALS to inform the potential further development of *tirasemtiv* in patients living with ALS.

References:

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4. University of San Francisco Memory and Aging Center. (2010) UCSF Memory & Aging Website. Retrieved from <http://memory.ucsf.edu/Education/Disease/als.html>
5. Data on file

About Us

Cytokinetics is a clinical-stage biopharmaceutical company focused on the discovery and development of novel small molecule therapeutics that modulate muscle function for the potential treatment of serious diseases and medical conditions. Cytokinetics is developing *tirasemtiv*, a fast skeletal muscle activator, as a potential treatment for amyotrophic lateral sclerosis (ALS). *Tirasemtiv* has been granted orphan drug designation and fast track status by the U.S. Food and Drug Administration and orphan medicinal product designation by the European Medicines Agency for the potential treatment of ALS. Cytokinetics is collaborating with Amgen Inc. to develop *omecamtiv mecarbil*, a cardiac muscle activator, for the potential treatment of heart failure. Cytokinetics is collaborating with Astellas Pharma Inc. to develop CK-2127107, a skeletal muscle activator, for spinal muscular atrophy. Amgen holds an exclusive license worldwide to develop and commercialize *omecamtiv mecarbil* and Astellas holds an exclusive license worldwide to develop and commercialize CK-2127107. Both licenses are subject to Cytokinetics' specified development and commercialization participation rights. All of these drug candidates have arisen from Cytokinetics' muscle biology focused research activities and are directed towards the cytoskeleton. The cytoskeleton is a complex biological infrastructure that plays a fundamental role within every human cell. Additional information about Cytokinetics can be obtained at <http://www.cytokinetics.com/>.



Skeletal muscle contractility can be increased by activating skeletal troponin, the regulatory complex in the skeletal muscle sarcomere.



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