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First licensed stem cell therapy for ALS

CORESTEM launched the world's first stem cell therapy for amyotrophic lateral sclerosis in South Korea in 2015. The company is now seeking out-licensing partners as it works toward product approvals in the US and Europe.

CORESTEM is a biotechnology company specializing in the research and development of personalized stem cell therapies for neurological and autoimmune diseases. Its lead product is NeuroNata-R (lenzumestrocel), the world's first stem cell-based therapy for amyotrophic lateral sclerosis (ALS).

NeuroNata-R was approved as an orphan drug for the treatment of ALS by the Ministry of Food and Drug Safety (MFDS) in South Korea in 2014. "Back then there were no ground rules laid out by the MFDS for stem cell therapy, so CORESTEM has been paving the way in this regard, and the path we took was adopted by the MFDS as regulatory guidelines," said KyungSuk Kim, CEO of CORESTEM.

ALS, also known as Lou Gehrig's disease or motor neuron disease, is a progressive neurodegenerative disease that leads to muscle atrophy due to the death of motor neurons. The average life expectancy is three to five years after the onset of disease. The only approved treatments for ALS outside South Korea are the small-molecule drugs riluzole and edaravone.

NeuroNata-R is based on autologous bone marrow-derived mesenchymal stem cells (MSCs). Treatment involves extracting bone marrow from the patient, isolating and culturing MSCs, mixing with cerebrospinal fluid collected from the patient, and administering the final product by intrathecal injection. The first NeuroNata-R injection typically takes place four weeks after the first bone marrow extraction, followed by a second injection four weeks later.

Treatment with NeuroNata-R results in various effects that prevent motor neuron death and slow the progression of ALS[1–3] (**Fig. 1**). These include the release of immune-modulating factors, such as regulatory T lymphocytes and T helper 2 factors; a motor neuron protective effect through the expression of growth factors, such as brain-derived neurotrophic factor; and an anti-inflammatory effect due to microglial cells switching from an M1 to an M2 phenotype.

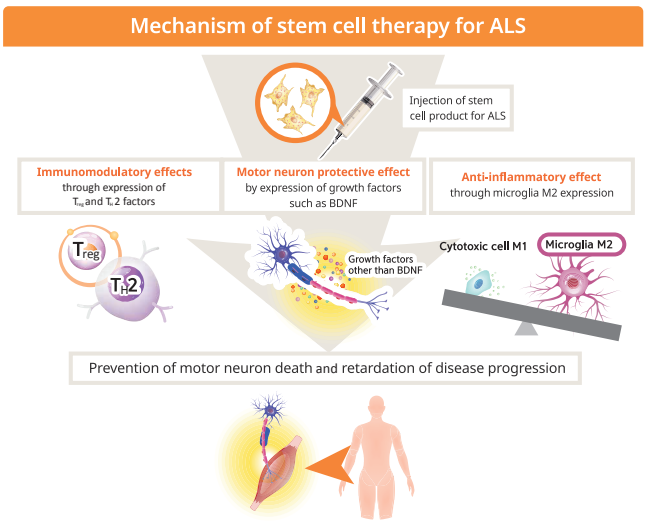

Fig. 1 | NeuroNata-R is a stem cell therapy approved in South Korea for ALS. NeuroNata-R has various effects that prevent motor neuron death and slow disease progression in patients with amyotrophic lateral sclerosis (ALS)[1–3]. BDNF, brain-derived neurotrophic factor; T_H2, T helper 2; T_{reg}, regulatory T.

Safety and efficacy data

Data from clinical studies show that NeuroNata-R slows the progression of ALS as measured by a change in ALS Functional Rating Scale-Revised (ALSFRS-R)[2,3].

A phase 1 open-label study demonstrated the safety and feasibility of two repeated intrathecal injections of autologous bone marrow-derived MSCs over twelve months in seven patients with ALS[2]. This was followed by a phase 2, parallel group, randomized controlled trial of two repeated intrathecal injections, which demonstrated safety and effectiveness for slowing the progression of ALS for at least six months[3]. Compared with the control group ($n = 27$), the mean changes from baseline ALSFRS-R score were significantly lower in the NeuroNata-R group ($n = 32$) at four months (group difference 2.98; 95% CI 1.48–4.47, $P < 0.001$) and at six months (3.38; 95% CI 1.23–5.54, $P = 0.003$)[3].

On the basis of phase 1 and 2 data, NeuroNata-R was approved in South Korea in July 2014 and launched in February 2015. By March 2019, 371 patients had received NeuroNata-R in South Korea (256 patients since commercialization), including 49 foreign patients.

CORESTEM is now preparing to conduct an innovative randomized, double-blind, placebo-controlled, multicenter phase 3 study to assess the safety and efficacy of NeuroNata-R in more than 94 patients with ALS. Patients will be randomized to receive two doses of study drug or placebo (cerebrospinal fluid without stem cells). A cryopreservation procedure will be developed so that ALS patients do not have to undergo repeat procedures for bone marrow extraction.

The primary outcome will be the change in ALSFRS-R from baseline to 24 weeks. Secondary outcomes will include other measures of function and quality of life. Eligible patients can take part in a supplementary study that will continue to week 48, and long-term efficacy and safety will be evaluated during an observation period of 36 months from the date of the first NeuroNata-R dose.

Partnering opportunities

CORESTEM has pioneered the development of innovative stem cell technology since it was founded in South Korea in 2003. The company was reorganized in 2015 in order to bring its first commercialized product onto the local market, and to design a strategy for accessing the global market.

NeuroNata-R received an orphan drug designation for the treatment of ALS from the US Food & Drug Administration (FDA) in 2018 and from the European Medicines Agency in early 2019. CORESTEM is now preparing the data package for a meeting with the FDA in the second quarter of 2019.

As CORESTEM works toward approvals for NeuroNata-R in the US and Europe, it is looking for out-licensing opportunities. "We are looking for partners who share our belief in the therapeutic potential of stem cells, who may be considering adding a stem cell therapy and/or a gene therapy to their pipeline," said Kim.

Alongside NeuroNata-R, CORESTEM is also progressing the clinical development of stem cell therapies for lupus nephritis and multiple system atrophy (both phase 1) and a pipeline of preclinical candidates.

1. Beers, D. R. et al. *Brain* **134**, 1293–1314 (2011).
2. Oh, K. W. et al. *Stem Cells Transl. Med.* **4**, 590–597 (2015).
3. Oh, K. W. et al. *Ann. Neurol.* **84**, 361–373 (2018).

contact
KyungSuk Kim, CEO
CORESTEM
Seongnam-si, Gyeonggi-do, Korea
Tel: +82 2 497 3711
Email: corestem@corestem.com