The inflammatory response is primarily driven by Interleukin-1. Anakinra is a recombinant protein produced by GlaxoSmithKline to inhibit this receptor. Arimoclomol is a small molecule that upregulates molecular chaperones in cells under stress, extending survival by five weeks when given both pre-symptomatically and at disease onset in a mutant form of ALS. Arundic acid (ONO-2506) is an agent that modulates astrocytes; it was believed to be neuroprotective because of its ability to decrease glutamate levels near nerves. Studies of ceftriaxone in the laboratory suggest that it may protect against neuronal death in ALS, and its safety and efficacy in this disease were explored in a clinical trial completed by Novo Nordisk.

CoQ10 is a natural compound that improves mitochondrial function and has shown neuroprotective effects in animal models of ALS. A CoQ10 Clinical Trial of High Dose CoQ10 in ALS was completed by Columbia University and the National Institute of Neurological Disorders and Stroke (NINDS). The study was designed to assess changes in strength in the arms and second by changes in grip strength, functional activities, electromyography changes or changes of the level of consciousness. The conclusion was that creatine monohydrate (5 g/d) did not have an obvious benefit on the multiple markers of disease progression in ALS. Other agents, such as tamoxifen, which is an autophagy activator, should be considered for further investigation.

Dexpramipexole is a potential therapeutic for ALS, and its safety, tolerability, and pharmacodynamic effects were evaluated in a study completed by Biogen Idec. The study was randomized and double-blind, and it assessed the pharmacodynamic effect of Dexpramipexole on measures of sleep and muscle strength in patients with ALS. The study was "likely to reach the predetermined efficacy criteria." Other therapeutic agents, such as creatine and tamoxifen, should be explored for their potential benefits in ALS.
### The primary objective of the study

The primary objective of the study is to extend the recruiting NCT00931944 II Interventional Non randomized Safety Open label Treatment Knopp Neurosciences USA Merit Cudkowicz 90 300 mg total daily dose for up to 180 weeks.

**Nat Med. 2011 Nov 20;17(12):1652-6. doi: 10.1038/nm .2579.**

Cudkowicz M, Bozik ME, Ingersoll EW, Miller R, Mitsumoto H, Shefner J, Moore DH, Schoenfeld D, Mather JL,

### A 2-Part, Randomized, Double-Blind, Safety and Tolerability Study Evaluating KNS-760704 in Patients With Dexpramipexole

Archibald D, Sullivan M, Amburgey C, Moritz J, Gribkoff VK.

In cell-based assays, both RPPX and PPX reduce the production of reactive oxygen species (ROS), attenuate the activation of apoptotic pathways, and increase cell survival in response to a variety of neurotoxins. However, this open label extension study to ALS patients who have participated in earlier clinical protocols.

### R(+) PPX Futility Study of R(+) Pramipexole in Early Amyotrophic Lateral Sclerosis

Decline of the ALS Functional Rating Scale-Revised (ALSFRS-R) in part 1 and a statistically significant (P = 0.046)

### Temporarily not found in myelin basic protein. The mechanism of action for glatiramer is unknown, although several have been shown to shift the population of T cells from pro-inflammatory Th1 cells to regulatory Th2 cells that suppress the immune response.

### Completed NCT00424463 III Interventional Randomized Safety/Efficacy Double blind Treatment Mitsubishi Tanabe Pharma Corporation Japan Koji Abe 181 group, Placebo-controlled Manner.

### Completed NCT00326625 II Interventional Randomized Safety/Efficacy Double blind Treatment Teva Pharmaceutical Industries Europe/Israele Merav Bassan 300 Pre-filled syringe, 40 mg, administered subcutaneously,

### GM604 GM604 Phase 2A Randomized Double-blind Placebo Controlled Pilot Trial in Amyotrophic Lateral Disease (ALS)

Multifactorial, and single target drugs are ineffective. The study drug is an regulatory peptide with a sequence neurotrophic factor, and a highly attractive candidate for the treatment of neurodegenerative conditions such as ALS.

### Completed NCT00397423 II Interventional Randomized Safety/Efficacy Double blind Treatment Peking University China Dongsheng Fan 40

### Efficacy, Safety and Tolerability of Growth Hormone in IGFR-1

IGF-1

### Efficacy of Lithium Carbonate in Subjects With Amyotrophic Lateral Sclerosis

Survival in patients with ALS treated with lithium and combination with riluzole slows progression of ALS more than riluzole alone.

### Edaravone (2.3+/-3.6 points) was significantly less than that in the six months prior to edaravone administration (4.7+/-2.1 of the six-month treatment period. Data from the present study suggest that edaravone is safe and may delay progression.

### An Expanded Controlled Study of MCI-186 for Treatment

Fingolimod (Gilenya) in Amyotrophic Lateral Sclerosis (ALS)

G-CSF

### Riluzole 14 days, followed by 14 days observation period (first 14 days, then 14 days observation period)

### Genervon Biopharmaceuticals, LLC

Hiroshi Mitsumoto, Merit Cudkowicz 12

### ISIS 333611 was well tolerated when administered as an intrathecal infusion. Antisense oligonucleotides delivered to the CNS might be a feasible treatment for neurological disorders.

### A Phase 1, Double-Blind, Placebo-Controlled, Dose-Escalation Study of the Safety, Tolerability, and Pharmacokinetics of ISIS 333611 Administered Intrathecally to Patients With Familial Amyotrophic Lateral Sclerosis

Mutations

### Memantine but we cannot exclude a positive outcome on survival.

### Efficacy of Memantine With Riluzole (Customary Care) for the Treatment of ALS Completed NCT01020331 II Interventional Randomized Safety/Efficacy Open label Treatment Phoenix Neurological Associates, LTD Forest Laboratories USA Todd Levine 20 10 mg twice a day
Mexiletine is a use-dependent sodium channel blocker that has been FDA-approved for decades for the treatment of nerve pain. It is commonly used at a dose of 50 mg two to three times per day for 12 weeks.

In the laboratory of Dr. Robert Brown at the University of Massachusetts, it has been demonstrated that Mexiletine, when administered at a dose of 300 milligrams/900 milligrams/placebo by mouth to patients with Amyotrophic Lateral Sclerosis (ALS), can significantly improve functional outcomes as detected by the ALS Functional Rating Scale (ALSFRS-R).

Cohort 1: 0.3 mg/kg NP001 (6:2 active:placebo) Cohort 2: 1.1 mg/kg NP001 (6:2 active:placebo) Cohort 3: 2.1 mg/kg NP001 (6:2 active:placebo)

In a Phase 2 Randomized, Double-Blind, Placebo-Controlled, and 15 mg) Administered Once Daily in Patients With Amyotrophic Lateral Sclerosis.

CONCLUSION: The trial revealed no evidence of a beneficial effect of TCH346 on disease progression in patients with ALS.

A Phase 1A Randomized, Double-Blind, Placebo-Controlled, and Safety and Dose Escalating Study of Oral Sodium Phenylbutyrate in Subjects With Amyotrophic Lateral Sclerosis (ALS). Patients Treated With Riluzole (MITOTARGET).

Familial ALS patients taking pyrimethamine will show a slower rate of disease progression as assessed by the ALSFRS-R score deterioration.

The primary outcome measure will be the safety assessment. [Time Frame: Safety assessment will be evaluated through follow-up visits after the end of treatment and 6 months after the last dose of the study drug.]
Vascular Endothelial Growth Factor

sNN0029

A Safety and Tolerability Study of Intracerebroventricular Administration of sNN0029 to Patients With Amyotrophic Lateral Sclerosis

Completed NCT00800501 I/II Interventional Randomized Safety Double blind Treatment NeuroNova AB

Medtronic

ICON Clinical Research Belgium

Wim Robberecht

Continuous ICV infusion at one of three dose levels or placebo for 3 months

Safety and tolerability through assessment of adverse events, ECGs, vital signs, clinical laboratory variables, MRI of brain and spinal cord, CSF sampling, and device performance as characterized by catheter tip placement and infusion accuracy (every 3 months)

dec-08 giu-11 dec-11

VEGF is an endogenous human protein fundamental to the development of the vascular and nervous systems

Vascular Endothelial Growth Factor A Activator

SB-509

A Phase 2 Repeat-Dosing Clinical Trial of SB-509 in Subjects With Amyotrophic Lateral Sclerosis

Completed NCT00748501 II Interventional Randomized Safety/Efficacy Open label Treatment Sangamo Biosciences USA

Ely Benaim

45

Cohort 1: SB-509 60 mg drug administration via IM injection of neck, arms, and legs; Two doses on Day 0 and Day 90. Cohort 2: SB-509 drug 60 mg administration via IM injection of legs; Two doses on Day 0 and Day 90.

Progression of the disease in subjects with ALS, as measured by ALSFRS-R sep-08 jun-10 oct-12

SB-509 contains the gene for a protein; injections of SB-509 into the neck, arms and/or legs muscles causes these tissue cells to make a protein. This protein increase the production of one own protein called vascular endothelial growth factor (VEGF-A), which may improve structure and function of nerves and muscles.

YAM80

Pilot-Study of YAM80 in Amyotrophic Lateral Sclerosis. Evaluation of the Efficacy and Safety of YAM80 in Amyotrophic Lateral Sclerosis (ALS)

Unknown NCT00886977 II Interventional Safety/Efficacy Open label Treatment Yoshino Neurology Clinic Japan

Hiide Yoshino

25

Oral administration, 2 to 6 mg, once a day. ALSFRS-R [Time Frame: 24w + follow-up period] apr-09 dec-10 oct-10

Zinc and copper

Zn-Cu Phase 1 Open Label Study of Zinc Therapy in ALS Patients

Completed NCT01259050 I Interventional Randomized Safety/Efficacy Open label Treatment Phoenix Neurological Associates, LTD USA

Todd D Levine

David S Saperstein

10

Optizinc 90 mg/d Copper 1 mg

To evaluate the safety of high doses of zinc in patients with ALS [Time Frame: 1 year] oct-10 mar-12 mar-12

Since it is known that SOD1 binds zinc, and many of the mutant forms of this enzyme associated with ALS show altered zinc binding, zinc may play a key role in all pathological processes associated with ALS. Previous studies have shown that in ALS mutant G93A SOD transgenic mice, actual zinc supplementation delayed death. Zinc has also been thought to serve as an endogenous antioxidant in the central nervous system and help protect the BBB against oxidative stress. BMAA (β-methylamino-L-alanine and glutamate) a neurotoxin and glutamate would be kept in a bound complex with zinc, i.e. eliminating competitive binding for zinc, which lead to less excitotoxic free glutamate and glutamate toxicity would be reduced.