HEALEY ALS Platform Trial

Investigational Products Tested in the Trial

Zilucoplan

February 25, 2021

Merit Cudkowicz, MD
Principal Investigator

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

Sabrina Paganoni, MD, PhD
Co-Principal Investigator

Accelerating ALS Therapy Development

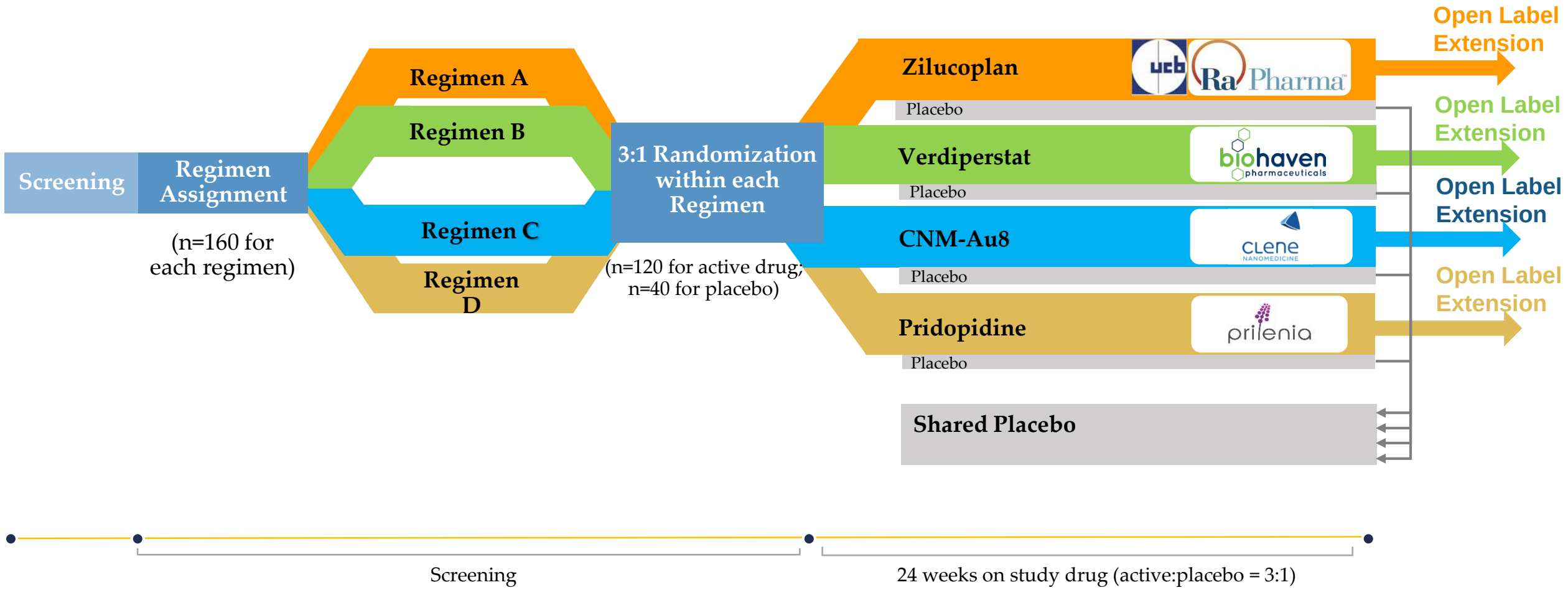
Traditional

	Intervention
Disease	Treatment A

Platform

	Intervention			
Disease	Treatment A	Treatment B	Treatment C	Treatment D

Perpetual Adaptive Trial
Randomization Ratio 3:1; Shared Placebo
Open Label Extension offered



Regimen Leads

Sabrina Paganoni, MD, PhD
MGH, Boston, MA
Regimen Lead

Christina Fournier, MD
Emory University, Atlanta, GA
Regimen co-Lead

Complement Inhibition in Amyotrophic Lateral Sclerosis

Camil Sayegh, PhD

UCB, Inc.

Zilucoplan is an investigational drug product that has not been approved for any use by the U.S. Food and Drug Administration. This information is being provided pursuant to an unsolicited request for scientific information. This presentation is not intended to provide medical advice

Complement Inhibition

Complement is part of the innate immune system

- Complement can be activated by antibodies or foreign cells, including bacteria
- In some diseases, including IMNM, complement can be activated by auto-antibodies, which leads to tissue damage
- Zilucoplan is understood to inhibit the cleavage of complement component C5 into C5a and C5b, thereby inhibiting the terminal complement pathway including formation of the membrane attack complex and strong proinflammatory signals
  - C5a is a proinflammatory ‘anaphylatoxin’
  - C5b associates with C6, C7, C8 and C9 to form the membrane attack complex (MAC) which is a hydrophilic pore that inserts itself into membranes and can lead to cell lysis

Zilucoplan: Potential as a Self-Administered, Subcutaneous, Macrocyclic Peptide Inhibitor of Complement C5

Zilucoplan is an investigational drug product that has not been approved for any use by the U.S. Food and Drug Administration.

Multiple indications, pipeline-in-a-product potential

Alternative Pathway

Activated by non-self cells

C3

Factor D, Factor B

Classical Pathway

Activated by antibody-antigen complexes

C1q – C1r – C1s

Lectin Pathway

Activated by pathogen surfaces

C5

C5a

Proinflammatory cytokine

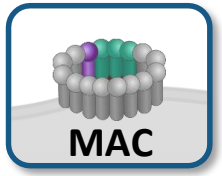
C5b

C6

C5b6

C7, C8, C9

Membrane attack complex (MAC)



Zilucoplan (SC)

Binds C5, blocks cleavage; Blocks MAC assembly

15 amino-acid cyclic peptide inhibitor of C5

Multiple Indications

gMG: Phase 2 positive
Phase 3 ongoing

IMNM: Phase 2 ongoing

ALS: Platform trial ongoing

PNH: Phase 2 positive

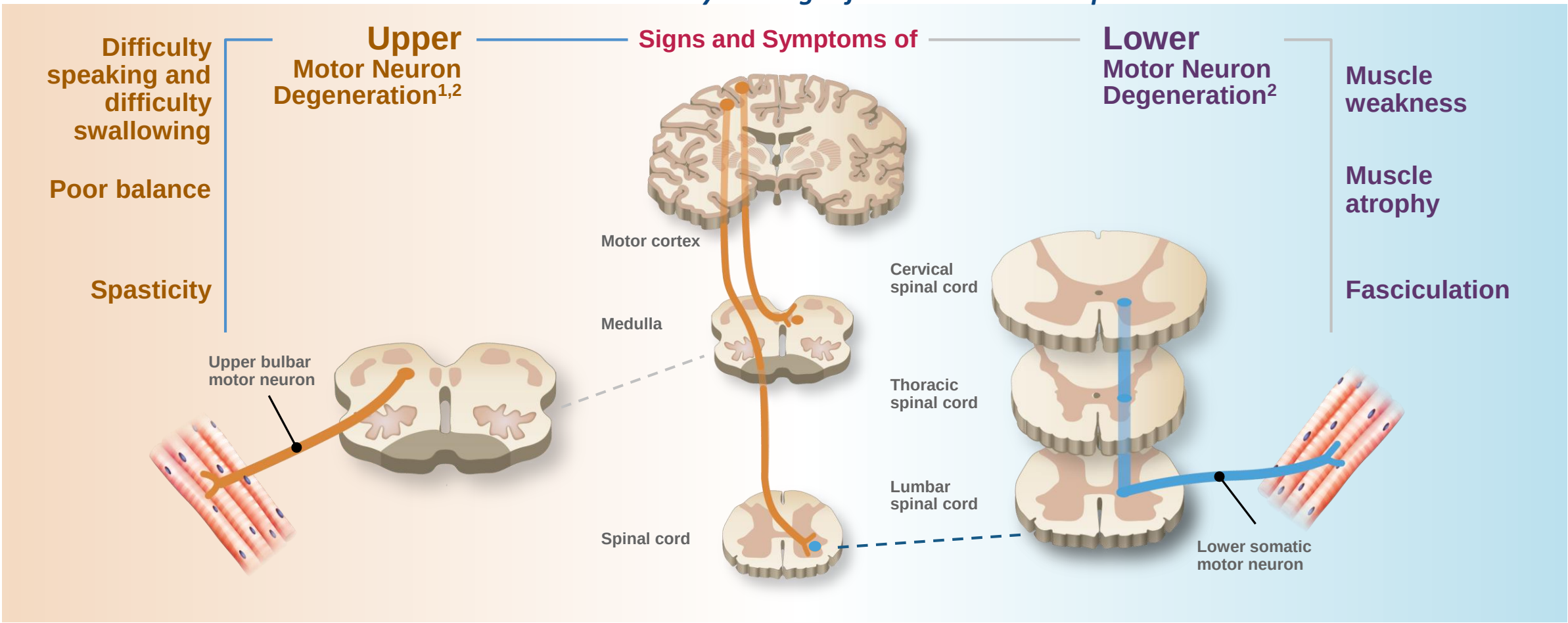
Renal Disorders: Phase 1b positive

gMG – generalized myasthenia gravis; IMNM – immune-mediated necrotizing myopathy; ALS – amyotrophic lateral sclerosis; PNH – paroxysmal nocturnal hemoglobinuria

The Neuropathological Hallmark of ALS Is the Loss of Upper and Lower Motor Neurons[1]

Neurodegeneration involves upper (corticospinal) and lower (ventral horn and cranial nerve nuclei) motor neurons[1].

Motor neurons are nerve cells that carry messages from the brain and spinal cord to muscles.



ALS, amyotrophic lateral sclerosis.

1. Hardiman O, et al. *Nat Rev Dis Primers*. 2017;3:17071. 2. Muscular Dystrophy Association. Amyotrophic lateral sclerosis: signs and symptoms. https://www.mda.org/disease/amyotrophic-lateral-sclerosis/signs-and-symptoms. Accessed April 6, 2020.

Preclinical Studies Suggest an Important Role for Terminal Complement Components in ALS Pathophysiology

The expression of terminal complement components is upregulated compared to healthy controls

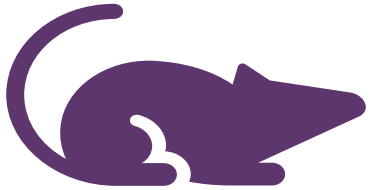
↑ C5aR1 with disease progression in lumbar spinal cord[1] and tibialis anterior muscle[2]

↑ C5a in tibialis anterior muscle[2]

↑ MAC deposition on motor endplates[3]

↑ CD59a (inhibitory regulator of MAC formation) in the lumbar spinal cord[1] and tibialis anterior muscle[2]

Expression Studies



$SOD1^{G93A}$
ALS mouse model

Inhibition of C5a-C5aR1 signaling reverses disease progression

Genetic deletion of C5aR1 reversed denervation of neuromuscular junctions and improved motor deficits[2]

Administration of C5aR1 antagonist significantly extended survival and slowed disease progression[4]

Genetic deletion of C5aR1 extended survival[5]

Ablation Studies

These findings are limited to preclinical data in animals.

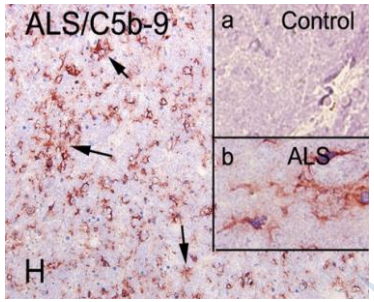
ALS, amyotrophic lateral sclerosis; C5aR1, complement component 5a receptor; CD59, cluster of differentiation 59; MAC, membrane attack complex; SOD1, superoxide dismutase type-1.

1. Lee JD, *et al. J Neuroinflamm* 2013;10:119; 2. Wang HA, *et al. Skeletal Muscle* 2017;7:10; 3. Bahia El Idrissi N, *et al. J Neuroinflammation* 2016;13:72; 4. Lee JD, *et al. Br J Pharmacol* 2017;174:689; 5. Woodruff TM, *et al. Proc Natl Acad Sci* 2014;111:E3–4.

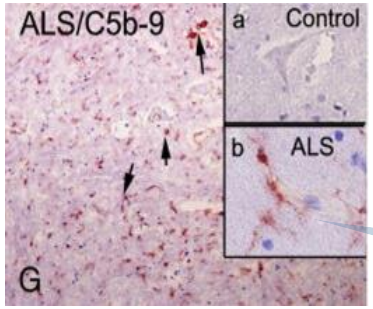
Complement MAC Proteins Are Associated With Neuroinflammation in Patients With ALS

Activation of the immune system, including a high expression of complement proteins, has been observed in the spinal cord and motor neurons of patients with ALS[1,2]

White matter of spinothalamic tract



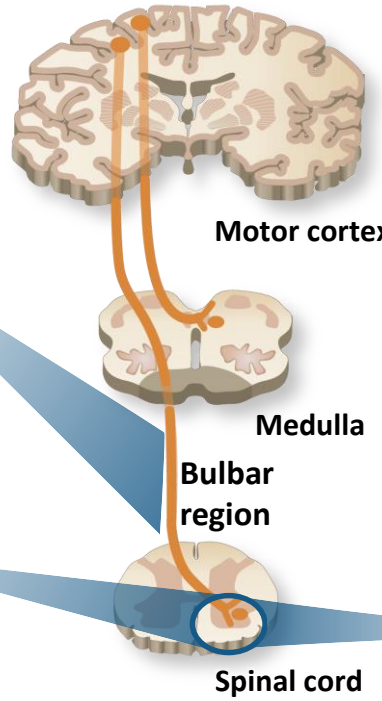
Glial cells of ventral horn



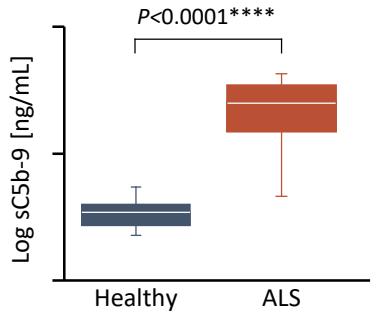
Arrows indicate positive MAC staining on glial cells

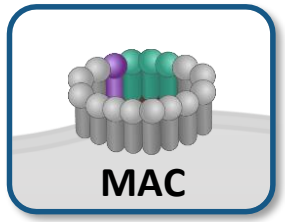
C5b-9 (MAC) detected in glial cells associated with the motor neurons of the spinal cord of patients with ALS, which is absent in healthy controls

Upper motor neurons



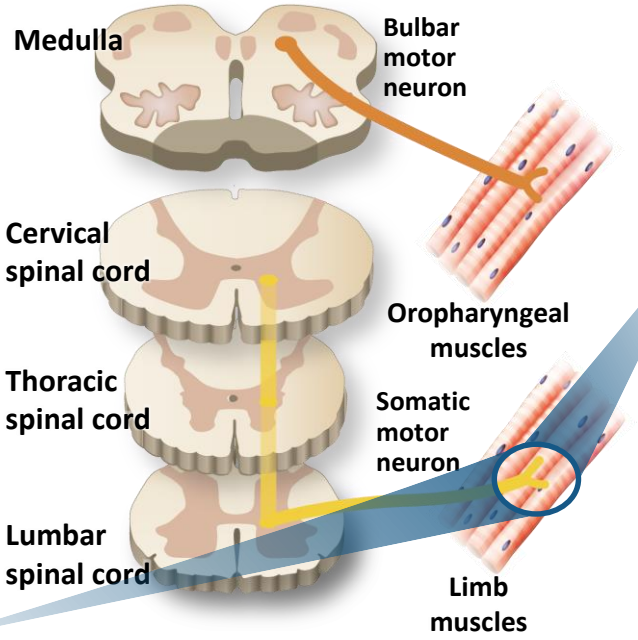
sC5b-9 in serum samples



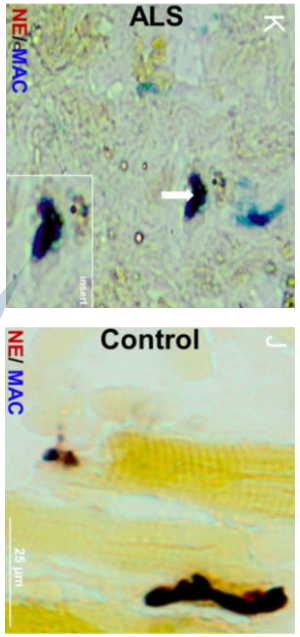


Complement activation and MAC deposition

Lower motor neurons



Motor end plates



MAC detected on the innervated motor end plates of intercostal muscle from patients with ALS, which is absent in healthy controls

P value calculated using a nonparametric Wilcoxon rank-sum test. sC5b-9, serum complement components C5b through C9, also known as membrane attack complex (MAC).

1. Sta M, et al. *Neurobiol Dis*. 2011;42:211–220. **2.** Bahia El Idrissi N, et al. *J Neuroinflammation*. 2016;13:72. **3.** Kjældgaard A, et al. *Molecular Immunology*. 2018;102:14-25.

Questions?

For More Updates

- **Weekly webinars**

  The idea of came from our Patient Advisory Committee: we are excited to be talking with you on a weekly basis and take any questions you might have

- **Find the schedule and registration links on our website**

https://www.massgeneral.org/neurology/als/research/platform-trial-news/