Acute effects of riluzole and retigabine on axonal excitability in patients with ALS: a randomized, double-blind, placebo-controlled, three-way cross-over trial

***Jules AAC Heuberger*[1]*, Maria O Kovalchuk[2], Boudewijn THM Sleutjes[2], Dimitrios Ziagkos[1], Juan Chavez[3], Leonard van de Berg[2], Toby A Ferguson[3], Hessel Franssen[2], Geert Jan Groeneveld[1]**

[1]Centre for Human Drug Research, Leiden, the Netherlands; [2]University Medical Center Utrecht, Department of Neurology, Utrecht, the Netherlands; [3]Biogen, Department of Neurology Research and Early Clinical Development, Cambridge, United States

Introduction

Hyperexcitability of the motor neuronal system observed in ALS can be measured by peripheral motor nerve excitability testing.[1] The degree of abnormal excitability correlates with patient survival.[2] Riluzole treatment was previously shown to partially normalize excitability parameters in patients with ALS[3] and the potassium channel Kv7 activator retigabine reduces abnormal membrane excitability and improves cell survival *in vitro*.[4]

Aim

To evaluate acute effects of riluzole and retigabine on peripheral motor nerve excitability-testing and validate the method as a proof-of-pharmacology biomarker in patients with ALS.

Methods

This was a randomized, double blind, 3-way cross-over, placebo controlled study in 18 patients with ALS, aged 18 to 80 years with fasciculations in the arm as a clinical sign of peripheral hyper-excitability, thenar CMAP on distal median nerve stimulation of more than 1mV and no carpal tunnel syndrome. Patients already on riluzole were asked to withhold intake starting 24 hours prior to study drug administration. Each study day consisted of:

- Motor nerve excitability-testing at baseline, 1.5h and 6h after dosing
- A single dose of 100 mg riluzole, 300 mg retigabine or placebo
- Regular blood samples for pharmacokinetics

Results

Between- and within-day repeatability was acceptable or better for 14 of 18 excitability variables. Both riluzole and retigabine reached therapeutic concentrations, but no effects of riluzole on excitability test variables were observed.

Retigabine influenced the following variables compared to placebo:

- Increased hyperpolarizing I/V-slope (21.7%, 95% CI 3.5-43.0%), rheobase (28.0%, 95% CI 9.1-50.1%) and threshold for a 50% CMAP (25.0%, 95% CI 7.6-45.2%)
- Decreased strength-duration time-constant (9.2%, 95% CI 14.1-3.9%), refractory period (0.17ms, 95% CI 0.27-0.06ms) and refractoriness at 2ms (10.2 percent point, 95% CI 17.2-3.2 pp)

Conclusions

- Excitability-testing is a non-invasive method that is a reliable and repeatable biomarker in patients with ALS
- A single dose of retigabine has a larger effect on peripheral nerve excitability than a single dose of riluzole
- The acute effect of retigabine on excitability suggests partial reversal of previous abnormalities

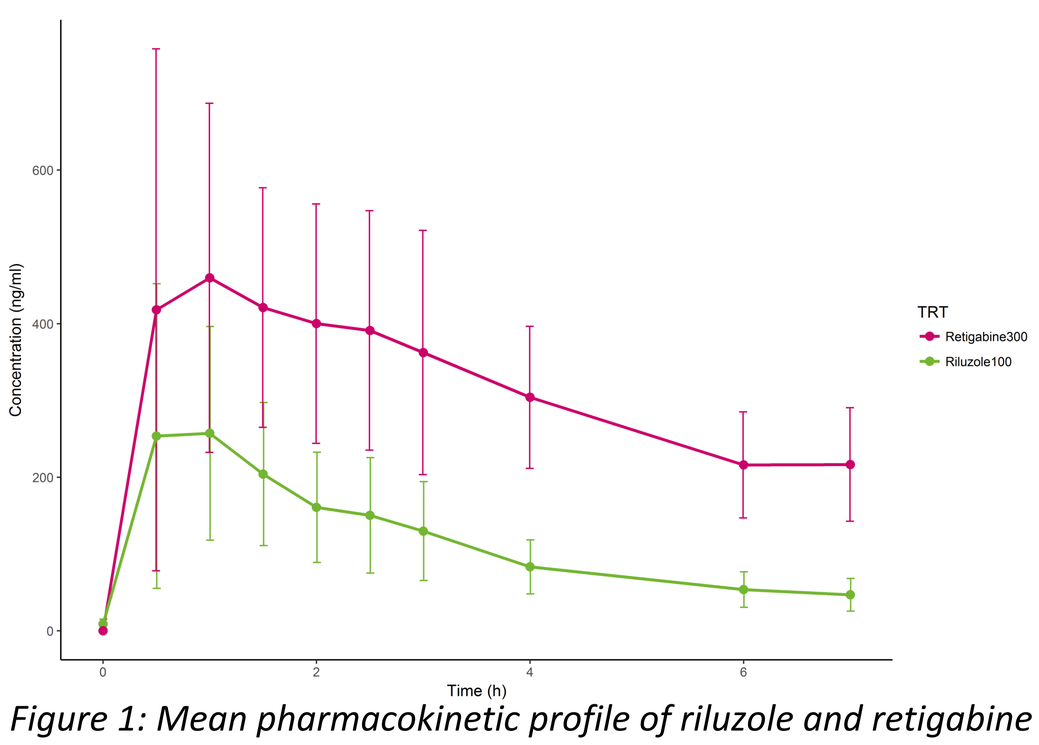

Figure 1: Mean pharmacokinetic profile of riluzole and retigabine

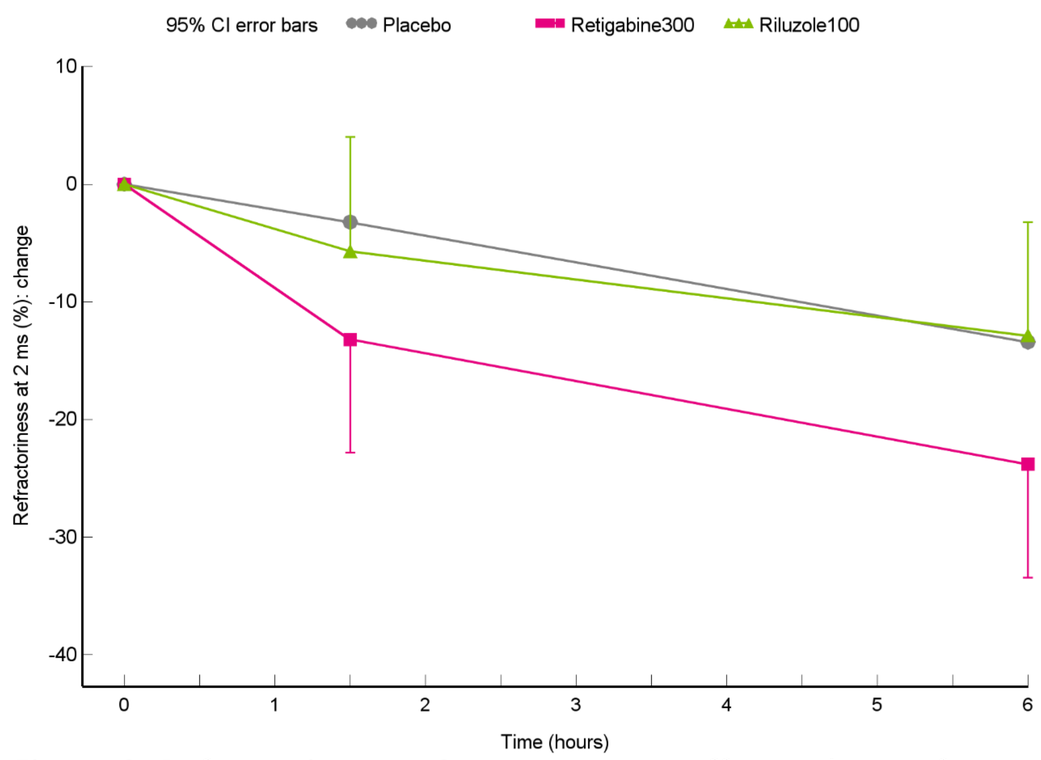

Figure 2: Refractoriness at 2 ms treatment effects, change from baseline

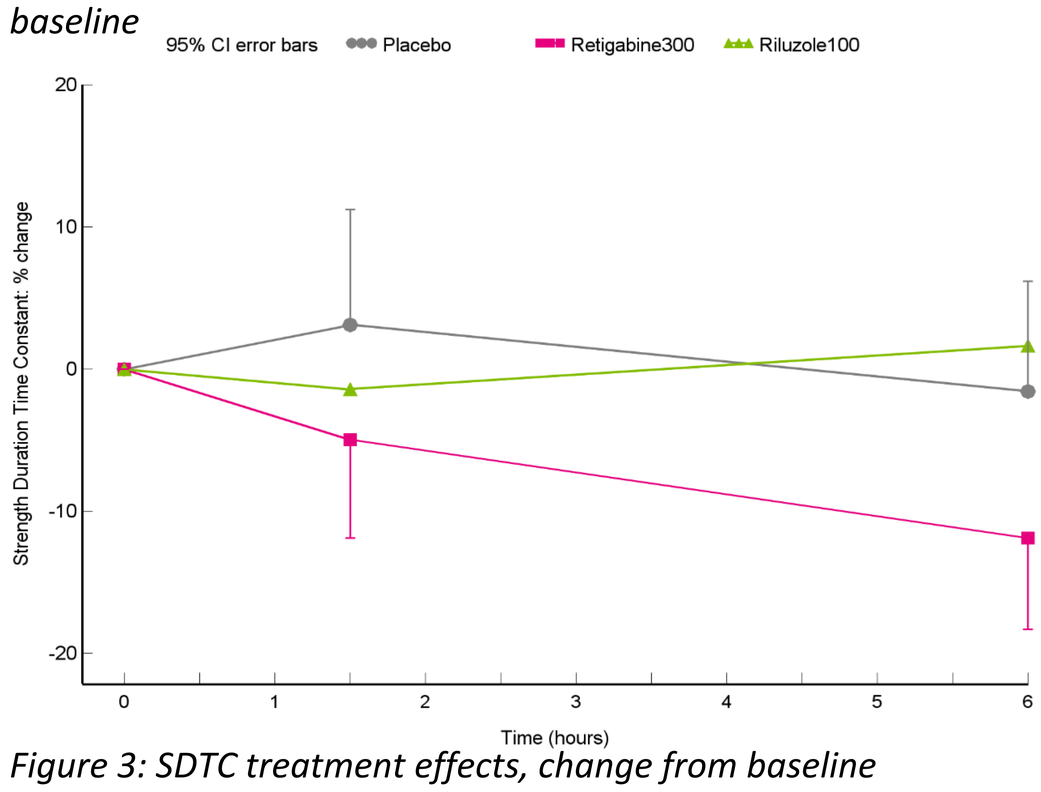

Figure 3: SDTC treatment effects, change from baseline

Centre for Human Drug Research | Zernikedreef 8 | 2333 CL Leiden | The Netherlands | Tel +31 71 52 46 400 | info@chdr.nl | www.chdr.nl

[1] Bostock H, Cikurel K, Burke D. Threshold tracking techniques in the study of human peripheral nerve. *Muscle Nerve* 1998;21(2):137-58.
[2] Kanai K, Shibuya K, Sato Y, et al. Motor axonal excitability properties are strong predictors for survival in ALS. *J Neurol Neurosurg Psychiatry* 2012;83(7):734-38.
[3] Vucic S, Lin CS, Cheah BC, et al. Riluzole exerts central and peripheral modulating effects in amyotrophic lateral sclerosis. *Brain* 2013;136(Pt 5):1361-70.
[4] Wainger BJ, Kiskinis E, Mellin C, et al. Intrinsic membrane hyperexcitability of amyotrophic lateral sclerosis patient-derived motor neurons. *Cell Rep* 2014;7(1):1-11.