Summary (Synopsis)

EudraCT: 2008-002110-22
Name of Sponsor: University Medical Centre Utrecht
Name of finished product: NA
Name of active ingredient: Lithium Carbonate
Individual study table, referring to part of the dossier, volume, page: J Neurol Neurosurg Psychiatry 2012;83:557e564, page 560.

Title of study: A randomised sequential trial of Lithium in amyotrophic lateral sclerosis
Investigators: Esther Verstraete, Jan H Veldink, Mark H B Huisman, Tim Draak, Esther V Uijtendaal, Anneke J van der Kooi, H Jurgen Schelhaas, Marianne de Visser, Ingeborg van der Tweel, Leonard H van den Berg
Study Centre(s): University Medical Centre Utrecht, Academic Medical Centre Amsterdam and Radboud University Medical Centre Nijmegen
Publication (reference): Neurol Neurosurg Psychiatry 2012;83:557e564. doi:10.1136/jnnp-2011-302021

Studied period (years): November 2008 and June 2011 (2 years and 7 months)
Date of first enrolment: November 2008
Date of last completed: June 2011
Phase of development: IIb

Objectives:
Primary objective: survival, defined as the time from inclusion to death, tracheostomal ventilation or non-invasive ventilation for more than 16 h/day.
Secondary objectives:
The rate of decline in daily functioning, measured by the validated revised ALS Functional Rating Scale (ALSFRS-R) and FVC (forced vital capacity)
To assess the effect of Lithium Carbonate versus placebo on thyroid function (thyroid stimulating hormone), kidney function (creatinine), electrolytes (sodium, potassium), liver enzymes (aminotransferase concentrations, alkaline phosphatase, g-glutamic transpeptidase) and leucocytes.

Methodology: This was a sequential, randomised (stratified and balanced 1:1 randomisation), double blind, placebo controlled, parallel group trial conducted in The Netherlands (three sites)
Number of patients (planned and analysed): 155 patients screened, 133 patients randomized, all randomized patients were analyzed for the primary endpoint
Diagnosis and main criteria for inclusion: Patients were eligible if they were diagnosed as having clinically probable laboratory supported, probable or definite ALS according to the World Federation of Neurology El Escorial.
Other inclusion criteria: use of riluzole (50 mg, twice daily); onset of symptoms at least 6 months and no longer than 36 months prior to inclusion; a forced vital capacity (FVC) of at least 70% of the predicted value based on gender, height and age (in the sitting position); age between 18 and 85 years; and written informed consent
Main exclusion criteria: tracheostomal ventilation of any type, non-invasive ventilation for more than 16 h/day or supplementary oxygen during the last 3 months prior to inclusion; any medical condition or intoxication known to have an association with motor neuron dysfunction which might confound or obscure the diagnosis of ALS; presence of any concomitant life-threatening disease or any disease or impairment likely to interfere with functional assessment; contraindications to lithium therapy (eg, confirmed renal insufficiency or cardiac arrhythmias); and other medication interacting with lithium with a significant risk of complications (eg, verapamil).

Test product, dose and mode of administration, batch number: Lithium carbonate orally (lithium carbonate 400 mg)

Duration of treatment:

In this trial there was no set duration of treatment as a sequential design was applied. A sequential design for a randomised controlled trial allows a series of interim analyses on the emerging data to be conducted and specifies the circumstances that determine when the trial will stop or continue at each analysis for efficacy, a harmful effect or futility. In this study, median follow-up was 16 months for the lithiumgroup (n=66) and 15 months for the placebo group (n=67) (IQR 2-31 months for both groups).

Reference therapy, dose and mode of administration, batch number: Placebo orally

Criteria for evaluation:
Efficacy: survival, defined as the time from inclusion to death, tracheostomal ventilation or non-invasive ventilation for more than 16 h/day
Safety: safety analysis was performed comparing the proportion of patients who had a serious adverse event in the lithium group with those in the placebo group. The safety boundary is determined by the hypothesised SAE rates for the lithium and placebo group as well as the risk of false alarm: alpha. An SAE rate of 0.25 was expected in the placebo group; an SAE rate of 0.40 or more in the lithium group was considered undesirable. The type I error a was set at 0.10 (one sided) as a warning when lithium would be unsafe.

Statistical methods: Sequential trial design. The trial was designed to detect a 15% increase in cumulative survival percentage in the lithium group, similar to the effect of riluzole.

Summary – Conclusions

Efficacy of Results: This study showed that lithium, in combination with riluzole, did not improve survival in patients with ALS.

Safety Results: Safety analyses did not reveal major safety issues but discontinuation of trial medication due to adverse effects occurred significantly more often in patients taking lithium compared with placebo.

Conclusion: this randomised, sequential, placebo controlled trial demonstrated the inefficacy of lithium for the treatment of ALS based on cumulative survival in a substantial cohort of patients.

Date of report: 20-12-2022