Author’s response to reviews

Title: Mecasin treatment in patients with amyotrophic lateral sclerosis: study protocol for a randomized controlled trial

Authors:

Sungha Kim (bozzol@kiom.re.kr)
Jae Kyoun Kim (jaekyoun.kim@gmail.com)
Mi Ju Son (mj714@kiom.re.kr)
Dongwoung Kim (dwkim@wonkwang.ac.kr)
Bongkeun Song (songbk@wku.ac.kr)
Ilhong Son (sonih@wku.ac.kr)
Hyung Won Kang (onp21@hanmail.net)
Jongdeok Lee (jdlee@wonkwang.ac.kr)
Sungchul Kim (kscndl@daum.net)

Version: 1 Date: 15 Nov 2017

Author’s response to reviews:

November 13, 2017

C.J.M. (Karin) Klijn
Editor
Trials

Dear Dr. C.J.M. (Karin) Klijn:

We would like to thank you and the reviewers Trials for reviewing our article and providing us with valuable suggestions that considerably improved our manuscript. We have incorporated all
suggestions in the revised manuscript and have provided point-by-point responses to the reviewers’ comments below.

Response to reviewers’ comments.

Reviewer: 1

1. The authors state that riluzole is the only FDA approved drug for ALS. This is inaccurate. The FDA has also approved Neudexta as well as Edaravone. Please revise.

   -> As the reviewer pointed out, we have revised the phrase (Page 2 line 3; page 3, lines 8-10; page 7 line 25).

2. The authors state that that riluzole treatment often results in serious adverse events. In my personal experience riluzole is an extremely safe drug with little to no side-effect. Literature also does not support the view that riluzole is an unsafe drug, see for instance Miller, et al. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2012 in which they state: "safety of the drug is not a major concern". The authors either need to revise this statement or provide evidence to the contrary.

   -> Thank you for pointing this out. We have revised the statement (Page 2 line 4; page 3, line 10).

3. The authors state that their previous experience with treating ALS patients with the herbal drug (modified jakyakgamchobuja-tang) and the apparently positive effect they observed, forms the basis for this trial They reference 7 papers describing these findings. The majority of these papers are in Korean and will therefore not be available to the readership of this journal. It would therefore be useful to have some more detail on what is meant by "progression of the disease was alleviated". Moreover, from the titles of references 7-13 it seems compounds other than modified
jakyakgamchobuja-tang were used, such as Trihexyphenidyl, Megestrol Acetate and processed Glycyrrhiza uralensis. The authors need to clarify.

-> We have clarified and described previous studies as the reviewer suggested (Page 3, lines 13-18).

4. The authors state that Mecasin, also known as KCHO-1, has shown neuro-protective and anti-neuroinflammatory effects and safety in in vitro and in vivo trials (references 14-20). With the exception of reference 20 it seems these papers provide little evidence suggesting that Mecasin would be beneficial to ALS. Moreover, reference 20 is a study in which Mecasin was given SOD1 mice. Although this is the oldest and therefore most commonly used animal model of ALS, it is under increases critism. ALS patients with mutations in SOD1 gene constitute only 1-2% of all ALS patients. Moreover, SOD1-ALS patients do not have TDP-43 which is now considered the hallmark of ALS. Simply put, consensus is that the SOD1 mouse is good model of SOD1 ALS, but has little relevance to the form ALS that affects >95% of all patients.

-> Thank you for pointing that out, however, previous retrospective chart reviews showed that combined therapy with the herbal drug alleviated the progression of the disease. Based on the overall previous studies, Korea FDA approved this study.

5. The amount of preclinical and clinical evidence that is presented in the abstract and background is limited and I am therefore quite skeptical whether is sufficient to proceed towards a human trial.

-> Thank you for pointing that out, however, any current drugs could not extend survival completely, only make patients’ symptoms deteriorate more slowly. As mentioned above, Korea FDA approved this study based on the overall previous studies, through ‘rare and incurable disease’ tract.

6. The authors state that they will exclude patients with ≤30% forced vital capacity. In general patients with vital capacity below 60% are referred to respiratory physician to discuss the possibility of (non)-invasive ventilation. The vast majority of patients with a vital capacity below 50% are on some form of ventilation. In many trials the need for ventilation is considered to be
an end-point. Commonly VC greater than 60% or 80% are required to be enrolled. What is the rationale for this cut-off?

-> Thank you for pointing that out. Cut-off point in ALS protocol are various; 20 % (NCT03214146), 40 % (NCT02716662), etc. In my personal experience, patients who can eat and swallow have a good prognosis, even though their FVC is low. In addition, patients who have undergone mechanical ventilation or tracheostomy are already excluded. Also the patients’ SPO2 and ETCO2 will be regularly monitored throughout the study to notice any signs of respiratory failure.

7. What do the authors think the influence will be of including patients in respiratory failure into the trial with regards to drop-out?

-> As mentioned above, patients who have undergone mechanical ventilation or tracheostomy are already excluded.

8. The authors will exclude patients with a number of other diseases. They also list frontotemporal dementia (FTD). This needs clarification. ALS and FTD are now commonly seen as the phenotypic extremes of a single disease spectrum. Roughly 5-10% of ALS patients also have FTD and up to 50% show signs of FTD without fulfilling the formal diagnostic criteria. In other words FTD is not a disease separate from ALS. Do the authors mean that they do not wish to include ALS patients with signs of FTD? If so, how will they assess cognition and behaviour? There is nothing in protocol on this.

-> Thank you for pointing that out, however, both ALS patients with frontal lobe dementia and those with Parkinson's disease should not be included in this trial, since such patients had not been tested in riluzole trial (Bensimon G, et al. N Engl J Med 1994;330:585-591). We excluded patients with communication difficulties. In addition, we have recruited patients who diagnosed as ALS based on electromyography findings after comprehensive examinations including MRI, biopsy, cerebrospinal fluid tests, blood tests, urine tests, and genetic tests at either a university or a general hospital. With the comprehensive examination and communication ability test, patients with FTD have been excluded (Page 5 line 2).
9. The authors should provide a power calculation. Considering the very short follow-up and limited size it is my impression will not have any power to detect a beneficial effect of Mecasin.

-> The previous clinical studies were retrospective chart reviews using combined therapy consisting of the herbal drug, acupuncture, pharmacopuncture, and needle-embedding therapy. Therefore, we couldn’t perform a power analysis. Also this trial is phase II-A to determine proper dosage of Mecasin. We have clarified this aspect in our revised manuscript (Page 3, lines 13-18; page 6 lines 15-16).

10. The rate of decline on the ALSFRS-R is highly variable between patients. The average decline is roughly 1 point per month, but with a considerable spread around this average. In a 12 week period patients would therefore be expected to decline by a total of 3 point over the course of the trial. Therefore the space to detect a difference between the groups will be very limited. A longer follow-up would be highly adviseable.

-> Thank you for pointing that out. There are two reasons to have a short follow-up. First, this trial is phase II-A to determine the proper dosage of Mecasin. We have clarified the aim of the trial in the revised manuscript (Page 2 lines 20-22; page 3 lines 20-23; page 4 lines 1-9; page 6 lines 15-16; page 11, lines 15-18). Second, the initial proposed period of the trial was 6 month. However, the Korea FDA recommended to reduce the study period considering the safety and short life expectancy of ALS patients. As per the recommendation, we have reduced the study period to 3 months. Now we’re planning phase II-B trial with longer follow-up as the reviewer suggested.

11. When looking at groups of ALS patients the decline on the ALSFRS-R is linear, however in the individual patient this is absolutely not the case. Patients may stabilize for extended periods of time. These so-called plateaus are not uncommon. Roughly 25% of patient do not show any decline during a 6 month period, see Bedlack, et al. Neurology. It is therefore likely that many patients will not show any decline at all within the time frame of this trial. Again, this will severly impact the chance of detecting an effect. Most ALS trial have a follow-up of 12 months. Why was this unusually short follow-up chosen?

-> As mentioned above, we have short follow-up considering the safety and short life expectancy of ALS and purpose of the study; to assess proper dosage of Mecasin. Next phase II-B trial will have a longer follow-up as the reviewer suggested.
12. Strength measurements using the MRC scale are notoriously unreliable. There is large inter- and intrarater variability. Moreover, the scale is not linear and it is therefore not used commonly as an outcome measure in trial. Why choose the MRC scale over MMT, HHD or other methods?

- Thank you for your comment. We couldn’t choose hand-held dynamometers (HHD) because the value could be various depending on the involved area. MRC scale is easy to assess, and the same assessor has measured MRC scale in this trial. However, we will study a phase II-B trial with more reliable scale as the reviewer suggested.

13. Why choose pain as secondary outcome measure? Pain is not a cardinal feature of ALS. Although it does occur, it is most commonly a secondary phenomenon and many patients will not have pain at all.

- Thank you for your comments. Even though pain is not a cardinal feature of ALS, pain has been reported to occur in nearly 70% of ALS during the course of the disease (Page 8, line 25). Vas Pain is one of the secondary outcomes. If Mecasin has no meaningful effects on pain, vas pain will be excluded in the next phase II-B trial.

14. In summary, my biggest concern is with the design (duration, number of cases, assumptions). Additionally, the preliminary evidence is to perform this trial is questionable based on the data provided.

- Thank you for your comments. We have addressed all these concerns regarding the design (duration, number of cases, assumption) in our revised manuscript and response letter (Response to reviewers’ comments, 9-11; page 2 lines 20-22; page 3 lines 20-23; page 4 lines 1-9; page 6 lines 15-16; page 11, lines 15-18).

Reviewer: 2

Methods

1. Sample size (page 7 line, 26)
"The primary purpose of this trial is to examine the efficacy and safety of Mecasin combined with the standard treatment, Riluzole, and to investigate the appropriate dosage for Mecasin. Considering a dropout rate of 20%, 12 participants will be assigned to each of the three groups."

And

Introduction: "we have more than 200 cases of ALS who prolonged the life expectancy after taking herbs consisting of Mecasin (..)"

Did the authors perform a power analysis? Based on 200 cases this should be possible - it may considerably improve the methods of the study. The authors should comment on this.

-> We apologize for the confusion. Previous clinical studies were retrospective chart reviews using combined therapy consisting of the herbal drug, acupuncture, pharmacopuncture, and needle-embedding therapy. Therefore, we couldn’t perform a power analysis. We have clarified this aspect in our revised manuscript (Page 3, lines 13-18; page 6 lines 15-16).

2. Primary outcome (page 8, line 57)

"The Primary outcome is the Korean version of the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised result after 12 weeks of treatment."

And

Abstract: "This trial will test the efficacy and safety of Mecasin in conjunction with standard treatment, Riluzole, for alleviating the functional decline in patients with ALS."

The authors may consider serial measurements and a longer trial duration; i.e. a combined end point of decline in ALSFRS-R and survival may be considered with the data they are collecting (e.g. the Combined Assessment of Function and Survival (CAF$S$). CAF$S$ ranks patients’ clinical outcomes based on survival time and change in the ALS Functional Rating Scale-Revised (ALSFRS-R) score.1,2

Any effect of a new drug may go undetected in a design with 12 weeks duration. Moreover, the clinical meaningfulness of a change in overall ALSFRS-R slope within this period is unclear.2

-> Thank you for pointing that out. There are two reasons for design with 12 weeks duration. First, this trial is phase II-A to determine the proper dosage of Mecasin. We have clarified the aim of the trial in the revised manuscript (Page 2 lines 20-22; page 3 lines 20-23; page 4 lines 1-9; page 6 lines 15-16; page 11, lines 15-18). Second, the initial proposed period of the trial was 6
Month. However, the Korea FDA recommended to reduce the study period considering the safety and short life expectancy of ALS patients. As per the recommendation, we have reduced the study period to 3 months. Now we’re planning phase II-B trial with longer duration as the reviewer suggested.

Minor issues

Abstract

1. (…) "Food and Drug Administration approved drug for ALS, provides minimal benefit, prolonging patient life by only 2-3 months and often resulting in severe adverse events."

Rilutek does not often result in severe adverse events - elevated liver enzymes may be transient, clinically relevant leucopenia or interstitial pneumonia rarely occurs - the authors should amend this sentence. For example in the introduction, the phrasing is better: "and the FDA has advised physicians to exercise caution when prescribing Riluzole to patients with a history of liver failure and other medical conditions."

-> Thank you for pointing this out. We have revised the statement (Page 2 line 4; page 3, line 10).

2. "We have more than 200 cases of ALS who prolonged the life expectancy after taking herbs consisting of Mecasin."

Could the authors shortly describe objective assessments that resulted in this observation (serial ALSFRS-R?)

-> We have clarified and described previous studies as the reviewer suggested (Page 3, lines 13-18).

3. "Secondary outcomes include results of (..) pulmonary function test (..) creatine kinase, and body weight"
Pulmonary function test: the authors should describe in the abstract which pulmonary function test will be used, as this is an important outcome measure in ALS trials.

-> We revised the manuscript as the reviewer suggested (Page 2, line 15).

Methods

Inclusion criteria

1. "The inclusion criteria are as follows: (1) men and women between the ages of 20 and 80 years; (2) a diagnosis of "laboratory supported probable", "probable" or "definite" ALS according to the revised El Escorial criteria [21]; (3) an Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRSR) score greater than 20; (4) treatment with 100 mg of Riluzole up to 3 months prior to screening; (5) the ability to visit the hospital alone or with the assistance of a caregiver; and (6) the ability to provide voluntary written informed consent."

The authors may consider a disease duration (of less than 12 months) as inclusion criterion in order to investigate the effect of Mecasin in a more heterogeneous group of ALS patients. With the proposed inclusion criteria the proportion of bulbar patients, and consequently the generalisability of results will probably be low. When mostly prevalent ALS cases (as opposed to incident cases) will be included a large proportion of patients will have a lower rate of progression which precludes the finding of a significant and clinical meaningful effect within 12 weeks.

-> Thank you for your comments. We have investigated a disease duration of all recruited patients. For generalization of the results, we will consider a disease duration in inclusion criterion in the next phase II-B trial, as the reviewer suggested.

Exclusion criteria

2."The exclusion criteria are as follows: (1) patients with ≤30% forced vital capacity; (2) patients with other neurological diseases, including fronto-temporal dementia"

The authors should add the criteria which will be/were used, if any, to diagnose FTD in ALS - (e.g. Revised Strong criteria 2016). 3

-> Thank you for your comments. We excluded patients with communication difficulties (Page 5 line 2). In addition, we have recruited patients who diagnosed as ALS based on
electromyography (EMG) findings after comprehensive examinations including MRI, biopsy, cerebrospinal fluid tests, blood tests, urine tests, and genetic tests at either a university or a general hospital. With the comprehensive examination and communication ability test, authors are sure that patients with FTD have been excluded. Unfortunately, “ALS-FTSD: Revised diagnostic criteria” was published after this study began. Authors now plan to study phase II-B trial, and we will apply this revised strong criteria.

Secondary outcomes
3. Hamilton Rating Scale for Depression (HRSD).
"As patients with ALS complain of depression as the disease progresses [28], the HRSD will be used to evaluate the severity of depression symptoms. The questionnaire consists of 68 items divided into four categories of 17 items each."

The authors should comment on time since diagnosis and time of inclusion: inclusion of ALS patients shortly after the diagnosis may result in false positives on this outcome measure due to the possibility of (transient) feelings of anxiety and depression, which are not uncommon in patients with ALS.4

-> We agree with the reviewer. All the recruited patients took Riluzole up to 3 months prior to screening. It indicates there are no patients who recruited shortly after the diagnosis. Nevertheless, we have investigated the time since diagnosis and time of inclusion of all recruited patients. We will clarify the time when presenting results.

4. "We will measure pulmonary function using spirometry (Spirolab, Medical International Research), forced expiratory volume in 1 s (FEV1), and its ratio to forced vital capacity (FVC)."

Forced vital capacity (FVC) has been used in many previous trial in ALS. Although FVC has good predictive power for ventilator-free survival, the cut-off value indicating a poor prognosis, lies within the normal range (>80% predicted), which is related to findings that relatively high VC values may be observed close to a clinical meaningful event (e.g., tracheostomy). The authors may consider other measures of respiratory muscle strength (i.e. sniff nasal inspiratory pressure and peak cough flow, if collected.5
Thank you for your comments. We will consider measuring respiratory muscle strength (i.e. sniff nasal inspiratory pressure and peak cough flow) in the next phase II-B trial, as the reviewer suggested.

Statistical analysis

5. "The covariates for the ANCOVA will include age, sex, K-ALSFRS-R score, pulmonary function test score, creatine phosphokinase level, body weight, muscle circumference, and the survey scores used in the secondary outcomes."

The authors may consider including bulbar onset in this analysis.

We revised the manuscript and will consider when analyzing the results (Page 10, line 4).

Discussion

1. "There are large variations in the reported annual incidence of ALS in Europe, Asia, and North America, ranging from 2.1 to 8.5 per 100,000 population, with prevalence rates of 1% to 7-8% [32]. Among the incurable diseases, ALS affects very few patients, (…)

The rationale for the first part of this paragraph is unclear to me and may be left out completely.

We have made the clarifications in our revised manuscript (Page 11, lines 10–11).

Trial status

1. "Recruitment for this trial opened in August 2016 and will close in July 2017. At the time of manuscript submission, the trial was in the recruitment phase."

The current date is 22th of September 2017- the authors should amend this.

We have revised the manuscript as the reviewer suggested (Page 11, line 21).

We sincerely hope that our revised manuscript now meets the requirements of your journal. We thank the editor and reviewers at Trials once again for the constructive review of our paper.
Sincerely yours,

Sungchul Kim, KMD, Ph.D.

Center of ALS/MND, Wonkwang University Gwangju Medical Hospital, 1140-23 Hyjae-ro, Nam-gu, Gwangju, 503-310, Republic of Korea

Tel: +82-62-670-6441