PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A study protocol for a randomised, double-blind, placebo-controlled study evaluating the Efficacy of cannabis-based Medicine Extract in slowing the disease pRogression of Amyotrophic Lateral sclerosis or motor neurone Disease: the EMERALD trial
AUTHORS	Urbi, Berzenn; Broadley, Simon; Bedlack, Richard; Russo, Ethan; Sabet, Arman

VERSION 1 – REVIEW

REVIEWER	Walter G Bradley Miller School of Medicine, University of Miami, Miami, FL, USA
REVIEW RETURNED	27-Feb-2019

GENERAL COMMENTS	This proposed trial of 15 v 15 active v placebo ALS patients is really a Phase 1 trial, and this should be indicated. Similar size trials in the literature do not offer similar optimistic power calculations. This needs to be reviewed by a qualified statistician, who reviews the quoted Edaravone paper to ensure that the same entry criteria etc are applied. The abstract should contain the entry criterion of symptom duration being < 2 years. It is unclear why the combination of CBD 25 mg and < 2 mg THC in each pill was chosen. It is unusual to publish the protocol for an ALS trial prior to completion of the trial and the publication of the results.

REVIEWER	Kirsten Müller-Vahl Hannover Medical School Germany KMV has received consultant's honoraria from Abide Therapeutics, Fundacion Canna, and Therapix Biosiences, and speaker's fees from Tilray, and is a consultant for Zynerba Pharmaceuticals, has received financial or material research support from the EU (FP7-HEALTH-2011 No. 278367, FP7-PEOPLE-2012-ITN No. 316978), the German Research Foundation (DFG: GZ MU 1527/3-1), the German Ministry of Education and Research (BMBF: 01KG1421), the National Institute of Mental Health (NIMH), Tourette Gesellschaft Deutschland e.V., Else-Kroner-Fresenius-Stiftung, and GW,

	Almirall, Abide Therapeutics, and Therapix Biosiences, consultant's honoraria from Abide Therapeutics and Therapix Biosiences, and royalties from Medizinisch Wissenschaftliche Verlagsgesellschaft Berlin and Kohlhammer.
REVIEW RETURNED	24-Mar-2019

GENERAL COMMENTS	In this manuscript the authors describe the protocol of an RCT that aims to investigate efficacy and safety of a cannabis-based extract in patients with ALS. In the protocol all relevant aspects of the study are described. The protocol is very well written and understandable. It includes the rationale of the study including an overview of the relevant literature and a hypothesis, why cannabis-based medicine might be effective in the treatment of this disease. Furthermore, possible conflicts of interest including involvement of the industry are mentioned. The statistical methods are described in detail. The study was registered in a trial registration (NCT03690791). I have only a few minor points the authors should take into consideration to further improve the manuscript: 1) It remains unclear, why the age range (25-75 years) was chosen. 2) the authors should mention, how use of “cannabis or cannabinoid-based medications within 30 days of study entry” will be checked (only by interview or using a THC urine test or….?) 3) It would be of interest of the reader to know, how the maximal dose of CBD:THC was defined. 4) Please say Nabiximols (Sativexs) instead of Sativex (Nabiximols) (comparable to THC(Marinol)), and use in the following Nabiximols instead of Sativex. 5) In the paragraph “Blinding” it is said that the packaging, label and appearance of the placebo and the study drug will be “similar”. However, it must be not similar, but identical.

REVIEWER	Alessio Signori University of Genova - Italy
REVIEW RETURNED	05-Jul-2019

GENERAL COMMENTS	Please define ALSFRS-R in extended form in the abstract.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Walter G Bradley
Institution and Country: Miller School of Medicine, University of Miami, Miami, FL, USA
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below

Q1.This proposed trial of 15 v 15 active v placebo ALS patients is really a Phase 1 trial, and this should be indicated.

Response: Thank you for your comment. EMERALD trial aims to demonstrate efficacy of CBM. This can be considered as Phase II/III trial.

The sample size calculation was reviewed by our team and we provide our process for the reviewer to assess. We have attached a file under "Response to Reviewer 1. Question 1" to describe our calculation process.

The sample size description in the manuscript has been amended to the following:
"To detect a clinically relevant difference of 3.0 points on the ALSFRS-R scale with a power of 90% at a significance level of 5% based on a two-sample t-test to compare treatment groups, it was calculated that a total sample size of 30 participants was required (G* Power version 3.1.9.2). Sample size estimation was based on results from the Edaravone MCI-186-19 trial39 as their study population is similar to the target population of this trial, i.e. <2 years since onset of first ALS symptom. A standard deviation result of 2.4 units on the ALSFRS-R scale was chosen as it represented the largest pre-treatment estimate from each of the treatment and control groups of Edaravone MCI-186-19 trial39 prior to observation or at baseline." (p. 13)

Q2. Similar size trials in the literature do not offer similar optimistic power calculations. This needs to be reviewed by a qualified statistician, who reviews the quoted Edaravone paper to ensure that the same entry criteria etc are applied.

Response: Thank you roar this comment. We have consulted a biostatistician and he reviewed our sample size calculation. We have presented the process of calculation (as above) for the reviewer to assess.

Q3. The abstract should contain the entry criterion of symptom duration being < 2 years.

Response: Thank you for this comment. The abstract has been amended to include symptom duration <2 years: “A total of 30 pALS with probable or definite ALS diagnosis based on El Escorial criteria with symptom duration <2 years, age between 25 and 75 and with at least 70% forced vital capacity (FVC) will be treated for 6 months.” (p. 2)

Q4. It is unclear why the combination of CBD 25 mg and < 2 mg THC in each pill was chosen.

Response: Urbi et al. (2019) published a systematic review of cannabinoids in ALS murine models. This review demonstrated efficacy of cannabinoids in prolonging survival in ALS mouse model. A high CBD, low THC formulation was chosen because this most closely resembles the preparation used in an animal model study (Moreno-Martet et al. 2014) which demonstrated prolonged survival. Also, a high CBD product reduces the potential psychoactive effects associated with THC. However, a small dose of THC is needed to potentially help with some of the symptoms (e.g spasticity and pain) commonly associated with ALS/MND.

“…when CBD and THC are combined, CBD potentiates the effects of THC while counteracting its psychoactive side effect (Devinsky et al. 2014). Additionally, CBD modulates the activation of CBRs (Russo 2011) and widens its therapeutic window which could affect significant improvement of survival and slowing of ALS progression. There are also known benefits of CBD such as anti-inflammatory, neuroprotective and anxiolytic properties (Devinsky et al. 2014). On this evidence, it can be argued that a clinical trial using a combined low THC and high CBD is the most appropriate intervention to investigate in patients with ALS.” (Urbi et al., 2019, p. 292)

CannTrust high CBD capsule (25mg CBD and <2mg THC) is the most available product the EMERALD study team is able to access in Australia for the trial. Other cannabis manufacturers (in Australia and overseas) were approached but they were either not ready to provide cannabis product

(including placebo) for clinical trial, or is unable to produce or time-delay in producing the products they say they can provide for our clinical trial.

The following was added under Investigational Product in the manuscript:

"A systematic review of cannabinoids in ALS murine models demonstrated the efficacy of cannabinoids in prolonging survival of SOD1-G93A mice. A high CBD, low THC formulation was chosen because this most closely resembles the preparation used in an animal model study which demonstrated prolonged survival." (p.9)

Q5. It is unusual to publish the protocol for an ALS trial prior to completion of the trial and the publication of the results.

Response: BMJ Open is committed to improving standards in medical research by supporting the publication of study protocols (Sucksmith, 2015). The scientific merits of publishing clinical trial protocols have been clearly demonstrated (Johnston, 2008; Li et al. 2016).

Reference:
1. Johnston, B (2008). Publishing study protocols. Injury Prevention 14:73.
2. Li, T., Boutron, I., Al-Shahi Salman, R., Cobo, E., Flemyng, E., Grimshaw, J. M., & Altman, D. G. (2016). Review and publication of protocol submissions to Trials - what have we learned in 10 years?. Trials, 18(1), 34. doi:10.1186/s13063-016-1743-0
3. Sucksmith, E. (2015). Introducing 'How to write and publish a Study Protocol' using BMJ's new eLearning programme: Research to Publication. Retrieved from https://blogs.bmj.com/bmjopen/2015/09/22/introducing-how-to-write-and-publish-a-study-protocol-using-bmjs-new-elearning-programme-research-to-publication/

Reviewer: 2

Reviewer Name: Kirsten Müller-Vahl
Institution and Country: Hannover Medical School, Germany

In this manuscript the authors describe the protocol of an RCT that aims to investigate efficacy and safety of a cannabis-based extract in patients with ALS.

In the protocol all relevant aspects of the study are described. The protocol is very well written and understandable. It includes the rationale of the study including an overview of the relevant literature and a hypothesis, why cannabis-based medicine might be effective in the treatment of this disease. Furthermore, possible conflicts of interest including involvement of the industry are mentioned. The statistical methods are described in detail. The study was registered in a trial registration (NCT03690791).

I have only a few minor points the authors should take into consideration to further improve the manuscript:

Q1) It remains unclear, why the age range (25-75 years) was chosen.

Response: We are grateful to the reviewer for noting this omission. We have added the following to the manuscript. "This age range was chosen because cannabis use may cause memory deficits for developing brain (up to 24 years old)27,28 and there is limited data on the safety of cannabis in the elderly." (p.7)

Q2) the authors should mention, how use of “cannabis or cannabinoid-based medications within 30 days of study entry” will be checked (only by interview or using a THC urine test or….?).

Response: Thank you for this suggestion. The following statement was added under Study Population:
“Prior randomisation, the study team will ask each patient if they have taken cannabis or cannabis-based medication within the last 30 days. Additionally, each patient will undergo a THC urine test prior randomisation. Patients who test positive for THC will be excluded.” (p.8)

Q3) It would be of interest of the reader to know, how the maximal dose of CBD:THC was defined.
Response: Thank you for this suggestion. The following has been added under dose and mode of administration section:
"The maximum dose was determined by balancing the expected dose range for therapeutic effects with doses associated with undesired side effects. The CBD oil to be used in this study consists of a 25mg:<2mg ratio of CBD and THC where the THC component is known to be the agent causing potential psychoactive side effects. The therapeutic range of CBD/THC products (for social anxiety disorder, epilepsy, and insomnia) was found to be 150-600mg of CBD/day. This equates to <12mg to <48mg of THC of the study drug. However, as little as 2.5-3.0mg of pure THC in a single bolus has been reported to cause psychoactive effects in cannabis naïve patients35. We expect to be able to avoid low-dose THC psychoactive side effects as 1.) THC is combined with CBD which is known to mitigate the psychoactive effects of THC and 2.) the daily dose will be given bid or tds (split between two doses 8-12 hours apart). In addition, we will employ the “start low go slow” rationale to increase the dose into the likely therapeutic range thus allowing for adaptation by patients to potential side effects. The Clinical Guidance: for the use of medicinal cannabis products in Queensland, where this trial is being conducted, suggests a maximum dose of 32.4mg/day of THC for Sativex and 40mg of THC for Marinol. The investigators set <30mg of THC as the maximum dose for our trial. This is a conservative maximum dose but is still expected to produce therapeutic results." (p.10)

Q4) Please say Nabiximols (Sativexs) instead of Sativex (Nabiximols) (comparable to THC(Marinol)), and use in the following Nabiximols instead of Sativex.

BU: As per BMJ writing guideline: Whenever possible, drugs should be given their approved generic name. Where a proprietary (brand) name is used, it should begin with a capital letter. We thank the reviewer for spotting the oversight in our manuscript.

“Sativex (Nabiximols)” was changed to “nabiximols (Sativex)”, and “Sativex” changed to “nabiximols” in titration period section (p. 10)

Q5) In the paragraph “Blinding” it is said that the packaging, label and appearance of the placebo and the study drug will be “similar”. However, it must be not similar, but identical.

Response: Thank you again for this comment. The following section was amended to:

“To ensure blinding of investigators and participants to study treatment, the study drug or placebo will be provided in identical packaging and label. Due to some natural variability in the colour of the study drug, which is batch dependent, the colour of the placebo has been matched to be the same as the average colour of the study drug.” (p. 12)

Reviewer: 3

Reviewer Name: Alessio Signori
Institution and Country: University of Genova - Italy
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below

Please define ALSFRS-R in extended form in the abstract.
Response: Thank you for your comment. “ALSFRS-S” modified to “ALS Functional Rating Scale-Revised (ALSFRS-R)” in the abstract (p. 2)

Figure 1. Sample size estimate from Abe et al. (2017).

Statistical analysis

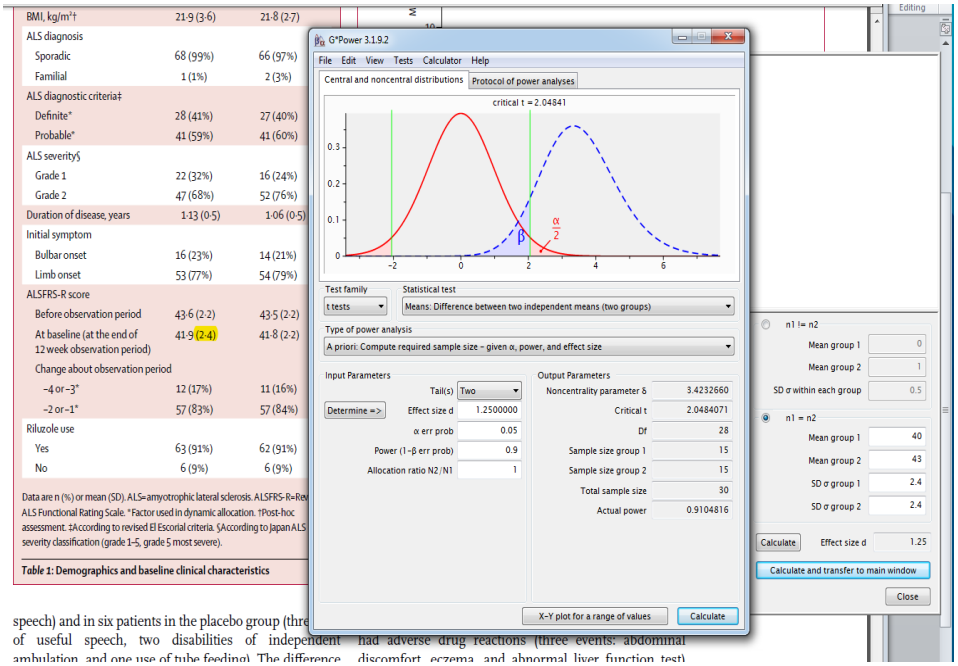
Based on the post-hoc findings in the previous phase 3 study, we calculated that a sample size of 128 patients (64 per group) was required to provide 80% power to detect an adjusted mean difference between groups of 3·0 points on the ALSFRS-R score at cycle 6 (24 weeks) with an SD of 6·0 points for analysis of the primary endpoint.

Figure 2. Results from Abe et al. (2017) showing standard deviations of ALSFRS-R prior to treatment.

ALSFRS-R score		
Before observation period	43·6 (2·2)	43·5 (2·2)
At baseline (at the end of 12 week observation period)	41·9 (2·4)	41·8 (2·2)
Change about observation period		
−4 or −3*	12 (17%)	11 (16%)
−2 or −1*	57 (83%)	57 (84%)

*Our final sample size calculation, conducted in G*Power, is shown in the screenshot in Fig. 3 overlaying the standard deviation results from Abe et al. (2017).*

Figure 3. Our sample size estimation.



VERSION 2 – REVIEW

REVIEWER	Kirsten Müller-Vahl Hannover Medical School Germany KMV has nonfinancial competing interests as a member of the TAA medical advisory board, the scientific advisory board of the German Tourette Association TGD, the board of directors of the German (ACM) and the International (IACM) Association for Cannabinoid Medicines, and the committee of experts for narcotic drugs at the federal opium bureau of the Federal Institute for Drugs and Medical Devices (BfArM) in Germany; has received financial or material research support from the EU (FP7-HEALTH-2011 No. 278367, FP7-PEOPLE-2012-ITN No. 316978), the German Research Foundation (DFG: GZ MU 1527/3-1), the German Ministry of Education and Research (BMBF: 01KG1421), the National Institute of Mental Health (NIMH), the Tourette Gesellschaft Deutschland e.V., the Else-Kroner-Fresenius-Stiftung, and GW, Almirall, Abide Therapeutics, and Therapix Biosiences; has served as a guest editor for Frontiers in Neurology on the research topic “The neurobiology and genetics of Gilles de la Tourette syndrome: new avenues through large-scale collaborative projects”, is an associate editor for “Cannabis and Cannabinoid Research” and an Editorial Board Member of “Medical Cannabis and Cannabinoids”; has received consultant's honoraria from Abide Therapeutics, Fundacion Canna, Therapix Biosiences, Tilray, Resalo Vertrieb GmbH, and Wayland Group, speaker’s fees from Tilray, PR Berater, Wayland Group, and Cogitando GmbH, and royalties from Medizinisch Wissenschaftliche Verlagsgesellschaft Berlin, Elsevier, and Kohlhammer; and is or was (during last 3 years) a consultant for Nuvelution TS Pharma, Inc., Zynerba Pharmaceuticals, Futrue

	GmbH, Apurano Pharmaceuticals GmbH, Syqe, Nomovo Pharma, and Columbia Care.
REVIEW RETURNED	13-Oct-2019

GENERAL COMMENTS	All comments have been addressed adequately. I have no further comments or concerns.

REVIEWER	Alessio Signori University Italy
REVIEW RETURNED	17-Oct-2019

GENERAL COMMENTS	-