



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Report for the RFI Application

A double-blind, randomized, placebo-controlled trial to test the efficacy, safety and tolerability of Dimethyl Fumarate in Friedreich Ataxia (DMF-FA-201).

2022-503016-16-00

Requests for information

Due date:

17/04/2023

Response date:

17/04/2023

Evaluation process:

Assessment Part I

MSC:

Italy

Changes made to the application:

No

RFI Unique Identifier:

CT-2022-503016-16-00-IN-007

RFI Status:

Responded

Date submitted:

14/04/2023

Consideration number:

1

Application section parts

Part I - Statistical

Application section and document:

Protocol

Consideration:

Considering that the cited effect size refers to increase of FXN/mRNA after DMF administration compared to fingolimod that are two different line of treatment for SM and moreover, as also defined by the researchers, the cited effect size is "very high effect size". A more conservative effect size would be preferable to reduce the probability of a negative or inconclusive study. Please justify the effect size chosen and the decision not to use a more conservative effect size

Sponsor response:

The effect size is now determined exclusively through our previously reported effect of DMF in Multiple Sclerosis patients (Hayashi et al., 2017). Since we are the authors of this paper and have access to the raw data, we found a partial eta square of 0.198 for the significant increase of FXN/mRNA after DMF administration compared to fingolimod (pseudo-placebo). Analysis was performed using a general linear model for repeated measures in SPSS. For sample size calculation, we entered the partial eta square value directly into G*Power software using the option "Effect size specification as in SPSS". This results in an effect size of 0.497. Final sample size is different than previously reported because of the different option used (it was previously selected as in "G*Power 3.0"). See software output attached for reference.

Estimating the effect size based on our preliminary data on MS patients is an underestimation of the potential effect of DMF in FRDA patients. Indeed, DMF can overexpress FXN through two mechanisms. One is the stimulation of nrf2 and the increase in transcription of several genes, including antioxidant genes and frataxin. This mechanism is clearly involved in MS patients treated with DMF and also in FRDA. The second mechanism is the ability of DMF to induce transcription initiation and reduce transcriptional pausing in mutant FXN gene. This mechanism is unique to FRDA patients as it requires a mutated gene to be effective. In support to this, experiments in patients' lymphoblasts treated with DMF have found up to a +260% increase relative to baseline (see reference 14], compared to our finding of +85% increase in MS patients treated with DMF. For this reason, we believe that an estimated effect size of 0.497 is appropriate for the use of DMF in FRDA and does not represent an overestimation of the potential effect of DMF in FRDA.