



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:

27/03/2023

Response date:

27/03/2023

Evaluation process:

Assessment Part I

MSC:

Italy

Changes made to the application:

Yes

RFI Unique Identifier:

CT-2022-503016-16-00-IN-003

RFI Status:

Responded

Date submitted:

15/03/2023

Consideration number:

1

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

Although the IMP already has marketing authorization for a different indication, the sponsor correctly declares that this trial is not classified as a low-intervention clinical trial. The Sponsor should address and discuss the rationale for the doses selected for the proposed study. Please amend the protocol accordingly;

Sponsor response:

Thank you for rising this point, we amended the protocol adding a comment on the reason for the treatment doses selected. They were chosen based on the approved doses for Multiple Sclerosis and based on our previous publication on the ability of this dose to significantly increase FXN/mRNA (section 3).

Consideration number:

2

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

A specific section on the benefit/risk assessment for the proposed trial is missing. The Sponsor is requested to add this specific section in the protocol, including measures to minimize the risk for the enrolled patients.

Sponsor response:

We amended the protocol adding a risk/benefit paragraph and the measures to minimize the risk of enrolled patients (section 10.10).

Consideration number:

3

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

Laboratory tests performed during the study should be listed in the protocol. Please amend the protocol accordingly.

Sponsor response:

Laboratory tests are reported in section 9.7 (Study Safety).

Consideration number:

4

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

Considering that the use of dimethyl fumarate is contraindicated during pregnancy and that animal studies have shown reproductive toxicity, the Sponsor is requested to amend the protocol according to CTFG recommendation on Contraception and pregnancy (21/09/2020) in order to include the following:

- a. The complete list of highly effective contraceptive measures required to the participants;
- b. The proper timelines for pregnancy test during the trial (including a test at the end of relevant systemic exposure).

Sponsor response:

We updated the protocol with highly effective birth control methods (section 10.11) and implemented the protocol with monthly pregnancy tests

Consideration number:

5

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

The Sponsor is requested to provide the rationale for the use of placebo.

Sponsor response:

The use of placebo is based on several factors. On one side the need for a more accurate evaluation on the biochemical effect on FXN/mRNA and frataxin, that can show fluctuations during time. For this reason, an increase of FXN/mRNA in an open-label trial could be erroneously attributed to treatment. The second reason is that secondary endpoints (CPET, Clinical scales, etc.) can show a clear placebo effect once patients take part to a clinical trial.

Consideration number:

6

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

The Sponsor is requested to justify the presence of valproic acid, Interferon-gamma, Erythropoietin and Etravirine among the prohibited therapies.

Sponsor response:

: Valproic acid, Interferon-gamma, Erythropoietin and Etravirine have been shown in-vitro, and partially in-vivo, to be able to increase frataxin protein. For this reason, we will exclude them from the trial. We added a comment in the protocol (section 7).

Consideration number:

7

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

The definition of the end of trial should be provided in the protocol. Please amend the protocol accordingly.

Sponsor response:

We now added a better definition of this in section 7 Intervention, subsection end of study.

Consideration number:

8

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

The Sponsor is requested to justify the absence of an upper age limit for enrolled patients.

Sponsor response:

We did not add an upper age limit as the natural history of Friedreich Ataxia shows a typical young onset (<18 years) and very few survive at higher ages (>50 years). We added a new upper age limit (<70 years) in section 6.1 inclusion criteria.

Consideration number:

9

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

Dimethyl fumarate is indicated for the treatment of adult and pediatric patients aged 13 years and older with relapsing remitting multiple sclerosis. In the proposed study, patients aged 12 years and older will be enrolled. Please clarify the discrepancy or amend the protocol.

Sponsor response:

Thank you for noticing the difference between approved age limit for Tecfidera (DMF approved for pediatric Multiple Sclerosis) and our trial. Several clinical trials have been conducted in pediatric Friedreich ataxia patients with lower age limits being 7, 10, 12, or 16 years of age. Non consensus is available on the most appropriate age limit, leaving the choice to the investigator. We previously validated the cardiopulmonary exercise test on Friedreich Ataxia patients with an age ≥ 12 years (Pane C, et al. Eur J Prev Cardiol 2022;29:445-451.) and performed a clinical trial using this as a primary endpoint with the same age limit (Saccà F, et al. Mov Disord 2016; 31:734-41.). We would like to keep the proposed age limit of 12 years of age as this trial proposes a new indication for DMF and previous approvals of DMF in Multiple Sclerosis are not related to the present medical condition. Also, no signals of increased adverse event have been reported in pediatric patients compared to adults. Friedreich Ataxia is a rare disease with many pediatric patients and trials should be as inclusive as possible to increase the generalizability of results.

Consideration number:

10

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

The Sponsor is requested to clarify if the PATA rate test is used to evaluate a secondary endpoint, as this test is mentioned in the Study Procedures Appendix, but is not described in the protocol.

Sponsor response:

We now added the Pata Rate Test in the secondary endpoint list and in the methods section (section 9).

Consideration number:

11

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

The Sponsor is requested to clarify the time-points for the evaluation of secondary endpoints.

Sponsor response:

We now added time-points for every secondary endpoint in section 8.2

Consideration number:

12

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

In case of co-primary endpoints, it is necessary to demonstrate an effect on each of the endpoints to conclude that a drug is effective. The Sponsor is requested to clarify the rational for considering the achievement of one out of two co-primary endpoints as a positive result.

Sponsor response:

The initial reason for two co-primary endpoints was based on the observation that some treatments (i.e. erythropoietin and Interferon-gamma) were able to increase frataxin protein without increasing FXN/mRNA. Thus, our initial approach was very conservative in considering the possibility of DMF to affect only one of the proposed endpoints. We re-evaluated our preliminary data, and already published data on DMF. The consistency of FXN increase led us to consider FXN/mRNA as the most stable and easy to measure endpoint. We are now considering it as the solely primary endpoint of the trial.

Consideration number:

13

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

Clinical trial termination criteria should be included in the protocol. Please amend the protocol accordingly.

Sponsor response:

We now added a better definition of this in section 7 Intervention, subsection end of study.

Consideration number:

14

Application section parts

Part I - Clinical

Application section and document:

Cover letter

Consideration:

The Cover letter should indicate in which document and section the Reference Safety Information (RSI) is contained. According to the EU regulation 536/2014, if it is proposed to use an IMP outside the (EU) indication of Marketing Authorization within the trial, section 4.8 of the SmPC for the IMP(s) could be used as the RSI, if scientifically justified by the sponsor in the clinical trial application cover letter. Otherwise, the RSI should always be a clearly separated specific section within the Investigator's Brochure. Applicant is requested to amend the Cover Letter, indicating the correct location of RSI (For more information, please refer to section 7.7 and following of Regulation (EU) No 536/2014 Questions & Answers – September 2022 - Version 6.2).

Sponsor response:

The RSI is contained in section 4.8 of SmPC "Effetti indesiderati", provided within the present application. The information is reported in the present cover letter in the section "the following information are communicated about the trial"

Consideration number:

15

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

According to the inclusion criteria patients with body weight ≥ 30 Kg will be enrolled. The Sponsor is requested to clarify the rational of the proposed cut off.

Sponsor response:

Body weight cut-off is based on the need for a linear relation and appropriate estimation of VO2 calculation at the CPET. We added a comment in section 9.3.

Consideration number:

16

Application section parts

Part I - Statistical

Application section and document:

Protocol

Consideration:

The statistical test adopted to the determination of the sample sizing is unclear. Please provide also the output of the determination of the sample sizing (with all the parameters involved) of the statistical software.

Sponsor response:

Thank you for pointing this out, we now revised the sample size calculation and provided all details in the protocol section 9.14.

Consideration number:

17

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

The criteria for dosing in minors (>12 years) must be specified. Please amend the protocol accordingly;

Sponsor response:

We amended the protocol section 6.

Consideration number:

18

Application section parts

Part I - Regulatory

Application section and document:

Deferral request

Consideration:

Phase 2 trial should belong to Category 2. Category 1 is not applicable for this clinical trial. Please correct the application form and the deferral request accordingly.

Sponsor response:

The application form and the deferral request was corrected

Consideration number:

22

Application section parts

Part I - Statistical

Application section and document:

Protocol

Consideration:

Inclusion of an expert medical Statistician in the trial team is strongly recommended.

Sponsor response:

We are grateful for this suggestion. The team already comprises experts in medical statistics with certified experience.

Consideration number:

23

Application section parts

Part I - Statistical

Application section and document:

Protocol

Consideration:

The sample size is calculated only considering one of the two endpoints (par.8). The sponsor is requested to consider both of the co-primary endpoints for the sample size calculation.

Sponsor response:

We now consider only one endpoint and provide sample size calculation for FXN/mRNA.

Consideration number:

26

Application section parts

Part I - Clinical

Application section and document:

Protocol

Consideration:

The criteria for deciding on how the dose is increased (up to the maximum) must be specified and the protocol must be modified accordingly.

Sponsor response:

There is no criteria for deciding on how dose is increased. As specified in section 7, all patients will receive 120 mg BID for the first week and then 2x 120 mg tablets BID for 11 weeks, the same is true for the extension phase. This is the standard administration scheme for Multiple Sclerosis.

Consideration number:

27

Application section parts

Part I - Statistical

Application section and document:

Protocol

Consideration:

According with the FDA 2022 biostatistics guideline for the Multiple Endpoints in Clinical Trials: Guidance for Industry, the co-primary endpoint definition seems to be in contrast with the decision rule based on the Demonstration of a Treatment Effect on at Least One of Multiple Endpoints. As was explained in point IIIC.2 of the aforesaid guideline, regarding the family of multiple primary endpoints a correction of the error rate is necessary in this last scenario. Actually, by an indicative estimation, the current sample sizing (not correctly evaluable in this protocol) is potentially underpowered (about 64%).

Sponsor response:

See previous point, now only one endpoint is being considered.

Consideration number:

28

Application section parts

Part I - Statistical

Application section and document:

Protocol

Consideration:

Although the study design and the endpoint underlie the comparison among the two treatments in terms of change during the time, the proposed measure in the sample size paragraph seems to refer only to the experimental group and its expected before-after delta. It is necessary to determine the sample size also taking into account the comparison between groups.

Sponsor response:

We now consider the sample size calculation using an ANOVA for repeated measures, within-between interaction, as the appropriate test (See protocol section 9.14).