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To
**Ufficio Sperimentazione Clinica
AIFA
Via del Tritone, 181
00187 Roma**

Roma, 27/03/2023

Object: EU CT number 2022-503016-16-00, Responses to RFI considerations of 15 January 2023

EudraCT number	2021-006274-23
EU CT number	2022-503016-16-00
Protocol Title	A double-blind, randomized, placebo-controlled trial to test the efficacy, safety and tolerability of Dimethyl Fumarate in Friedreich Ataxia.
Protocol Code	DMF-FA-201
Phase	II
Sponsor	Dipartimento di Neuroscienze, Scienze Riproduttive e Odontostomatologiche Università degli Studi di Napoli Federico II Via Sergio Pansini, 5 - 80131 Napoli, Italia
Applicant	Fullcro srl, Via Ignazio Guidi 5. 00147 Roma, Italia
Coordinator Site	UOS Centro Sclerosi Multipla AOU "Federico II" Via Pansini, 5 80131 Napoli

Fullcro srl, as representative of the Sponsor, replies to the RFI considerations in object with the following responses. As consequence, the application and the relevant documents sections of Form, Part I and Part II was updated.



PART I

Consideration number RFI-CT-2022-503016-16-00-IN-003-01

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 RFI-CT-2022-503016-16-00-IN-003-02

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 RFI-CT-2022-503016-16-00-IN-003-03

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 RFI-CT-2022-503016-16-00-IN-003-04

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 RFI-CT-2022-503016-16-00-IN-003-05

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 RFI-CT-2022-503016-16-00-IN-003-06

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 RFI-CT-2022-503016-16-00-IN-003-07

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 RFI-CT-2022-503016-16-00-IN-003-08

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 RFI-CT-2022-503016-16-00-IN-003-09

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 RFI-CT-2022-503016-16-00-IN-003-10

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 RFI-CT-2022-503016-16-00-IN-003-11

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 RFI-CT-2022-503016-16-00-IN-003-12

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 rationale 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 RFI-CT-2022-503016-16-00-IN-003-13

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 RFI-CT-2022-503016-16-00-IN-003-14

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 RFI-CT-2022-503016-16-00-IN-003-15

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

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 RFI-CT-2022-503016-16-00-IN-003-17

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 RFI-CT-2022-503016-16-00-IN-003-18

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 RFI-CT-2022-503016-16-00-IN-003-19

Consideration: The address for Industrias Farmacéuticas Almirall, (Sant Andreu de la Barca, Barcelona – Spain) is different between the one provided in the IMPD and that reported in the MIA. Please provide a clarification. .

Sponsor response: Recently, Sant Andreu de la Barca city hall has changed the name of the street where Almirall IFA SAB is placed. Therefore the center stills in the same place but the postal address has been



changed from Ctra Nacional II to Ctra Martorell. We provide the manufacturer authorization for Almirall centers including IFA SAB (doc: 20230214_ML IFA (2023) and the GMP certificate for IFA SAB (doc: ncf_2231-001_if_almirall), both stating the new address. It corresponds to the last –inspection conducted on May 2019. However, due to the COVID pandemic there is a general extension of the GMP certificates until the end of 2023.(Please find more information on the following link: [web de EudraGMP](#)) So that, the attached certificate is still valid. the address from IFA SAB in the IMPD was amended accordingly.

Consideration number RFI-CT-2022-503016-16-00-IN-003-20

Consideration: If any difference in specifications between the IMP and the marketed product occur, this should be specified and properly justified.

Sponsor response: Active medication is produced in the same line than commercial product but primary packaging is conducted in IFA SF to keep the same blister format than placebo medication. The placebo tablets are not produced in the commercial line (IFA SAB) but in the R&D center (IFA SF) from raw materials until primary packaging. The secondary packaging as well as labelling and kitting is conducted in Fundació DAU for both products. This is explained in the IMPD submitted to AIFA (see sections A3.1 and P3.1)

Regarding specifications, there are no changes between the IMPD and the commercial product.

Consideration number RFI-CT-2022-503016-16-00-IN-003-21

Consideration: The core label should report the following information: - directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product); - 'Keep out of reach of children', except when the product is for use in trials where the product is not taken home by subjects.

Sponsor response: Core labels were amended according your request

Consideration number RFI-CT-2022-503016-16-00-IN-003-22

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 RFI-CT-2022-503016-16-00-IN-003-23

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 RFI-CT-2022-503016-16-00-IN-003-24

Consideration: IMPD reports EudraCT number instead of EUCT number. Please correct accordingly.

Sponsor response: The IMPD has been amended as your request, anyway we wanted to pointed out that according to instruction provided in CTIS newsflash – 13 January 2023, the EudraCT Number is mandatory.

Consideration number RFI-CT-2022-503016-16-00-IN-003-25

Consideration: GMP documents for Laboratori Fundació Dau should be provided.

Sponsor response: The document is provided

Consideration number RFI-CT-2022-503016-16-00-IN-003-26

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: The 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 RFI-CT-2022-503016-16-00-IN-003-27

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 RFI-CT-2022-503016-16-00-IN-003-28

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).

PART II

Consideration number RFI-CT-2022-503016-16-00-IN-002-01

INFORMED CONSENT FORM – GENITORE Version 1.1 Jan 11, 2023 ASSENSO INFORMATO FINALIZZATO ALL'INSERIMENTO IN UNA SPERIMENTAZIONE CLINICA DESTINATO AD UN MINORE DI ETA' COMPRESA TRA 12 e 17 ANNI

Consideration: Questions/queries: Considering that we are addressing 12-17 year olds, we ask you to express the concept in a less "traumatic" way: Per quale ragione mi si chiede di partecipare a questa sperimentazione? Ti stiamo chiedendo di partecipare a una sperimentazione clinica finanziata da AIFA perché sei affetto/a da Atassia di Friedreich (FRDA), una malattia ereditaria caratterizzata da progressiva disabilità neurologica e cardiopatia.

Sponsor response: Thank you for your comment, we amended the sentence, both in consent for minor and parents

Consideration: Explain the expected benefits to the patient: Quali benefici posso aspettarmi? Partecipando a questo studio avrà la possibilità di sottoporsi ad un trattamento sperimentale innovativo dal quale si potranno ottenere informazioni importanti sull'efficacia del DMF nell'atassia di Friedreich. Tali informazioni permetteranno di accrescere le conoscenze scientifiche in modo che in futuro lei ed altre persone in simili condizioni possano avere maggiori risorse terapeutiche.

Sponsor response: Thank you for your comment, we amended the sentence, both in consent for minor and parents

Consideration: 1. There is a reference to a biobank, however, no information is provided regarding this structure: headquarter, responsible, duration. Furthermore, the specific consent for the biobank is not attached. In the absence of the specific documentation, it is necessary to remove this possibility. In case the documents for the Biobank are correct, it is necessary to explain that a specific informed consent will be submitted when future studies will be planned

Sponsor response: We are sorry for this typo, there is no biobank involved in this study. We corrected the IC accordingly and the reference to biobank has been removed.

Consideration: 2. There are references also to „genetic incidental findings“, but in the Protocol the analyses that will be performed are not completely described (mtDNA, nDNA, pathway of Nrf2). So, it is not possible to define if these analyses could have incidental findings

Sponsor response: There will be no genetic incidental findings as this is an expression study and the output cannot reveal "incidental findings". We amended the IC accordingly

Consideration: 3. It is not clear if the frataxin analysis will be performed „at the Mayo clinic“ or using „the Mayo clinic commercial test“ (see Protocol). So, it is not possible to define the correct information to the parents about the possible transfer of the biological sample.



Sponsor response: Frataxin protein will be measured at our center and not at the Mayo clinic laboratory service. We amended the IC and the protocol section 9.6.

Consideration: 4. Revise the term “Dimetyl fumarato” in “Dimetil fumarato”

Sponsor response: we corrected the typo

Consideration: 5. Add the information about the study of the other genes: expression studies?

Sponsor response: Yes, they are expression studies of genes mentioned in the secondary endpoints

Consideration: 6. Add the information about the place where the genetic analyses will be performed

Sponsor response: we specified that the analysis for genes expression will be performed at the site

Consideration: 7. Revise the term “vista “BASALE”” in “visita”

Sponsor response: we corrected the typo

Consideration: 8. Explain what means “randomizzazione”

Sponsor response: the explanation of term “randomizzazione” was already contained in the section “Quali sono i gruppi di pazienti a confronto? Quale è l’intervento in sperimentazione?”. We added the definition also in section “descrizione dello studio”, where it is mentioned for the first time.

Consideration: 9. Explain what means “test di funzionalità cardiopolmonare and test per valutare la reazione dei vasi sanguigni (FMD)”

Sponsor response: “test di funzionalità cardiopolmonare” has been explained in the document, FMD has been canceled as it will not be performed during the study, it was a typo

Consideration: 10. Explain what is “placebo”

Sponsor response: the explanation of term “placebo” was already contained in the section “Quali sono i gruppi di pazienti a confronto? Quale è l’intervento in sperimentazione?”. We added the definition also in section “descrizione dello studio”, where it is mentioned for the first time.

Consideration: 11. Remove the term “trattamento comparativo” in the phrase “trattamento conservativo/placebo”

Sponsor response: we removed the term “trattamento comparativo”

Consideration: 12. Clarify if the blood samples will be collected ad hoc for the study

Sponsor response: we specified that the biological samples “saranno prelevati e utilizzati ai fini della sperimentazioni”

Consideration: 13. It is not clear why the genetic analysis could show incidental findings: are they expression studies? Are there studies on germinal genes?

Sponsor response: they are expression studies of genes mentioned in the secondary endpoints, the reference to incidental findings has been removed

Consideration: 14. Remove the options regarding the destruction of data and samples “Non verranno distrutti solo nel caso in cui a) non sia più possibile ricondurli alla sua identità, perché anonimizzati nel corso della sperimentazione stessa; b) in presenza di uno specifico consenso informato”

Sponsor response: we removed these options

Consideration: 15. Add that in case of withdrawal biological samples will be destroyed

Sponsor response: we added this option in section “il consenso è definitivo?”

Consideration: 16. Explain where the biological analyses will be performed

Sponsor response: we added a sentence to clarify that the biological analyses will be performed at site

Consideration: 17. Add the option “non volere partecipare alla sperimentazione”

Sponsor response: we added this option in the consent form

Consideration number RFI-CT-2022-503016-16-00-IN-002-02

Consideration: Since the CRF was not available, it was not possible to complete this section: the CRF must be provided.

Sponsor response: the CRF was not provided as no specific section for CRF is foreseen in the CTIS. We uploaded the screen shot of last available draft, as the CRF will be finalized once the protocol will be approved, in the protocol documents section.



Consideration number RFI-CT-2022-503016-16-00-IN-002-03

Consideration: The insurance contract is in draft form and must be finalized before the trial starts. Confirmation that the insurance certificate will be made available before starting the trial must be provided.

Sponsor response: The Sponsor confirms that the insurance certificate will be made available before starting the trial, it is specified in the present cover letter in the section "the following information are communicated about the trial".

Consideration number RFI-CT-2022-503016-16-00-IN-002-04

Consideration: The document "Idoneità sito specifica" must be signed by the legal representative

Sponsor response: We provided "Idoneità sito specifica" signed by the legal representative

Consideration number RFI-CT-2022-503016-16-00-IN-002-05

INFORMED CONSENT FORM - MINORE Version 1.1 Jan 11, 2023 ASSENSO INFORMATO FINALIZZATO ALL'INSERIMENTO IN UNA SPERIMENTAZIONE CLINICA DESTINATO AD UN MINORE DI ETA' COMPRESA TRA 12 e 17 ANNI

Consideration: Questions/queries: Explain the expected benefits to the patient: Benefici attesi Partecipando a questo studio avrà/avrete la possibilità di sottoporre suo/vostro figlio/a/il minore ad un trattamento sperimentale innovativo dal quale si potranno ottenere informazioni importanti sull'efficacia del DMF nell'atassia di Friedreich. Tali informazioni permetteranno di accrescere le conoscenze scientifiche in modo che in futuro suo/vostro figlio/a/il minore ed altre persone in simili condizioni possano avere maggiori risorse terapeutiche.

Sponsor response: Thank you for your comment, we amended the sentence, both in consent for minor and parents

Consideration: Indicate that the insurance deductible will not be paid by the patient. La copertura assicurativa prevede un massimale di € 1.000.000,00 ed una franchigia di € 2.600,00.

Sponsor response: We specified that the insurance deductible will not be paid by the patient in the parents and adults consent, where the insurance is described

Consideration: Delete: "amministratore di sostegno".

Sponsor response: We deleted "amministratore di sostegno" in the parents consent, where is mentioned

Consideration: Delete: *Nel caso firmi un solo genitore, egli dichiara di essere consapevole di esprimere anche la volontà dell'altro genitore che esercita la responsabilità genitoriale - consapevole delle conseguenze amministrative e penali, per chi rilasci dichiarazioni non corrispondenti a verità a i sensi del DPR 445/2000, dichiara di aver effettuato la scelta in osservanza delle disposizioni sulla responsabilità genitoriale di cui agli articoli 316, 337 ter e 337 quater del codice civile, che richiedono il consenso di entrambi i genitori.

Sponsor response: We deleted "the sentence" in the parents consent, where it is present

Consideration 1: There is a reference to a biobank, however, no information is provided regarding this structure: headquarter, responsible, duration. Furthermore, the specific consent for the biobank is not attached. In the absence of the specific documentation, it is necessary to remove this possibility. In case the documents for the Biobank are correct, it is necessary to explain that a specific informed consent will be submitted when future studies will be planned

Sponsor response: We are sorry for this typo, there is no biobank involved in this study. We corrected the IC accordingly and the reference to biobank has been removed.

Consideration 2: There are references also to „genetic incidental findings“, but in the Protocol the analyses that will be performed are not completely described (mtDNA, nDNA, pathway of Nrf2). So, it is not possible to define if these analyses could have incidental findings

Sponsor response: There will be no genetic incidental findings as this is an expression study and the output cannot reveal "incidental findings". We amended the IC accordingly

Consideration 3: It is not clear if the frataxin analysis will be performed „at the Mayo clinic“ or using „the Mayo clinic commercial test“ (see Protocol). So, it is not possible to define the correct information to the parents about the possible transfer of the biological sample.



Sponsor response: Frataxin protein will be measured at our center and not at the Mayo clinic laboratory service. We amended the IC and the protocol section 9.6.

Consideration 4: Revise the term “Dimetyl fumarato” in “Dimetil fumarato”

Sponsor response: we corrected the typo

Consideration 5: Add the information about the study of the other genes: expression studies?

Sponsor response: Yes, they are expression studies of genes mentioned in the secondary endpoints

Consideration 6: Add the information about the place where the genetic analyses will be performed

Sponsor response: we specified that the analysis for genes expression will be performed at the site

Consideration 7: Revise the term “vista “BASALE”” in “visita”

Sponsor response: we corrected the typo

Consideration 8: Explain what means “randomizzazione”

Sponsor response: “Randomizzazione” is mentioned in the parents consent, the explanation of term “randomizzazione” was already contained in the section “Quali sono i gruppi di pazienti a confronto? Quale è l'intervento in sperimentazione?”. We added the definition also in section “descrizione dello studio”, where it is mentioned for the first time.

Consideration 9: Explain what means “test di funzionalità cardiopolmonare and test per valutare la reazione dei vasi sanguigni (FMD)”

Sponsor response: “test di funzionalità cardiopolmonare” has been explained in the document “ consenso genitore”, FMD has been canceled as it will not be performed during the study, it was a typo

Consideration 10: Explain what is “placebo”

Sponsor response: “Placebo” is mentioned in the parents consent, where the explanation of term “placebo” was already contained in the section “Quali sono i gruppi di pazienti a confronto? Quale è l'intervento in sperimentazione?”. We added the definition also in section “descrizione dello studio”, where it is mentioned for the first time.

Consideration 11: Remove the term “trattamento comparativo” in the phrase “trattamento conservativo/placebo”

Sponsor response: “ we removed the term “ trattamento comparativo” in the Parents consent, where it was mentioned

Consideration 12: Clarify if the blood samples will be collected ad hoc for the study

Sponsor response: in section “Trattamento dei campioni biologici “ we specified “Ai soli fini della sperimentazione vengono fatti dei prelievi di campioni biologici quali sangue e urine”

Consideration 13: It is not clear why the genetic analysis could show incidental findings: are they expression studies? Are there studies on germinal genes?

Sponsor response: they are expression studies of genes mentioned in the secondary endpoints, the reference to incidental findings has been removed

Consideration 14: Remove the options regarding the destruction of data and samples “Non verranno distrutti solo nel caso in cui a) non sia più possibile ricondurli alla sua identità, perché anonimizzati nel corso della sperimentazione stessa; b) in presenza di uno specifico consenso informato”

Sponsor response: we removed these options

Consideration 15: Add that in case of withdrawal biological samples will be destroyed

Sponsor response: we added this case in section “E se ad un certo punto volessi ritirarmi dalla sperimentazione?”

Consideration 16: Explain where the biological analyses will be performed

Sponsor response: in section Trattamento dei campioni biologici we added a sentence to clarify that the biological analyses will be performed at site

Consideration 17: Add the option “non volere partecipare alla sperimentazione”

Sponsor response: we added this option in the consent form

Consideration 18: Change the phrases “avrà la possibilità di sottoporsi” in “sottoporti”; “Lei ed altre persone” in “tu ed altre”

Sponsor response: we changed the phrases

Consideration number RFI-CT-2022-503016-16-00-IN-002-06



INFORMED CONSENT FORM - ADULTI Version 1.1 Jan 11, 2023 FOGLIO INFORMATIVO E MODULO DI CONSENSO INFORMATO PER LA PARTECIPAZIONE DEI PAZIENTI AD UNA SPERIMENTAZIONE CLINICA

Questions/queries:

Consideration: 1. There is a reference to a biobank, however, no information is provided regarding this structure: headquarter, responsible, duration. Furthermore, the specific consent for the biobank is not attached. In the absence of the specific documentation, it is necessary to remove this possibility. In case the documents for the Biobank are correct, it is necessary to explain that a specific informed consent will be submitted when future studies will be planned

Sponsor response: We are sorry for this typo, there is no biobank involved in this study. We corrected the IC accordingly and the reference to biobank has been removed.

Consideration: 2. There are references also to „genetic incidental findings“, but in the Protocol the analyses that will be performed are not completely described (mtDNA, nDNA, pathway of Nrf2). So, it is not possible to define if these analyses could have incidental findings

Sponsor response: There will be no genetic incidental findings as this is an expression study and the output cannot reveal “incidental findings”. We amended the IC accordingly

Consideration: 3. It is not clear if the frataxin analysis will be performed „at the Mayo clinic“ or using „the Mayo clinic commercial test“ (see Protocol). So, it is not possible to define the correct information to the parents about the possible transfer of the biological sample.

Sponsor response: Frataxin protein will be measured at our center and not at the Mayo clinic laboratory service. We amended the IC and the protocol section 9.6.

Consideration: 4. Revise the term “Dimetyl fumarato” in “Dimetil fumarato”

Sponsor response: we corrected the typo

Consideration: 5. Add the information about the study of the other genes: expression studies?

Sponsor response: Yes, they are expression studies of genes mentioned in the secondary endpoints

Consideration: 6. Add the information about the place where the genetic analyses will be performed

Sponsor response: we specified that the analysis for genes expression will be performed at the site

Consideration: 7. Revise the term “vista “BASALE”” in “visita”

Sponsor response: we corrected the typo

Consideration: 8. Explain what means “randomizzazione”

Sponsor response: the explanation of term “randomizzazione” was already contained in the section “Quali sono i gruppi di pazienti a confronto? Quale è l'intervento in sperimentazione?”. We added the definition also in section “descrizione dello studio”, where it is mentioned for the first time.

Consideration: 9. Explain what means “test di funzionalità cardiopolmonare and test per valutare la reazione dei vasi sanguigni (FMD)”

Sponsor response: “test di funzionalità cardiopolmonare” has been explained in the document, FMD has been canceled as it will not be performed during the study, it was a typo

Consideration: 10. Explain what is “placebo”

Sponsor response: the explanation of term “placebo” was already contained in the section “Quali sono i gruppi di pazienti a confronto? Quale è l'intervento in sperimentazione?”. We added the definition also in section “descrizione dello studio”, where it is mentioned for the first time.

Consideration: 11. Remove the term “trattamento comparativo” in the phrase “trattamento conservativo/placebo”

Sponsor response: we removed the term “trattamento comparativo”

Consideration: 12. Clarify if the blood samples will be collected ad hoc for the study

Sponsor response: in section 10 we specified that the biological samples “saranno prelevati e utilizzati ai fini della sperimentazione”

Consideration: 13. It is not clear why the genetic analysis could show incidental findings: are they expression studies? Are there studies on germinal genes?

Sponsor response: they are expression studies of genes mentioned in the secondary endpoints, the reference to incidental findings has been removed



Consideration: 14. Remove the options regarding the destruction of data and samples “Non verranno distrutti solo nel caso in cui a) non sia più possibile ricondurli alla sua identità, perché anonimizzati nel corso della sperimentazione stessa; b) in presenza di uno specifico consenso informato”

Sponsor response: we removed these options

Consideration: 15. Add that in case of withdrawal biological samples will be destroyed

Sponsor response: we added this option in section “ il consenso è definitivo?”

Consideration: 16. Explain where the biological analyses will be performed

Sponsor response: we added a sentence to clarify that the biological analyses will be performed at site

Consideration: 17. Add the option “non volere partecipare alla sperimentazione”

Sponsor response: we added this option in the consent form

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Consideration: There is a reference to a biobank, however, no information is provided regarding this structure: what about headquarter, responsible, storage time? Is there a specific consent for the biobank?

Sponsor response: We are sorry for this typo, there is no biobank involved in this study.

Consideration: Remove the phrases

- “Una volta scaduto il termine di conservazione sopra indicato, i dati verranno cancellati ovvero resi anonimi in modo che non sia più possibile risalire, in modo diretto o indiretto, all’identità dell’Interessato;

Sponsor response: This sentence was erroneously inserted in the section referring to the site, It has been moved in the section relevant to Sponsor

- Il titolare potrà comunicare o trasferire i dati dell’Interessato a enti e istituti di ricerca, alle associazioni e agli altri organismi pubblici e privati aventi finalità di ricerca, esclusivamente nell’ambito di progetti congiunti;

Sponsor response: The sentence has been removed

- Ove invece l’Interessato neghi il consenso al trattamento qui descritto, i dati verranno cancellati ovvero resi anonimi immediatamente allo scadere di termine di conservazione indicato al punto (A)”.

Sponsor response: : The sentence has been removed

- Delete “Il titolare potrà comunicare o trasferire i dati dell’Interessato a enti e istituti di ricerca, alle associazioni e agli altri organismi pubblici e privati aventi finalità di ricerca, esclusivamente nell’ambito di progetti congiunti.”

Sponsor response: : The sentence has been removed

- Delete “e all’ulteriore utilizzo”

Sponsor response: The sentence has been removed

Moreover, as requested, the following information are communicated about the trial:

- The trial is financed by AIFA, as specified in section “trial information-Source of monetary support or material support”
- The insurance fee will be paid as soon as the study approval will be obtained, and the insurance certificate will be made available before starting the trial
- The information, necessary for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction, is contained in the section 4.8 “Effetti indesiderati” of Skilarence 120 mg gastro-resistant tablets SmPC, provided within the present application.



- All the analysis foreseen by the protocol, including the analysis of gene expressions, will be performed at the investigational site.

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