



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 II

**MSC:**

Italy

**Changes made to the application:**

Yes

**RFI Unique Identifier:**

CT-2022-503016-16-00-IN-002

**RFI Status:**

Responded

**Date submitted:**

15/03/2024

**Consideration number:**

1

**Application section parts**

Part II - Italy

**Application section and document:**

Subject information and informed consent form

**Consideration:**

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

**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.

**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.

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
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
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
4. Revise the term “Dimetyl fumarato” in “Dimetil fumarato”
5. Add the information about the study of the other genes: expression studies?

6. Add the information about the place where the genetic analyses will be performed
7. Revise the term “vista “BASALE”” in “visita”
8. Explain what means “randomizzazione”
9. Explain what means “test di funzionalità cardiopolmonare and test per valutare la reazione dei vasi sanguigni (FMD)”
10. Explain what is “placebo”
11. Remove the term “trattamento comparativo” in the phrase “trattamento conservativo/placebo”
12. Clarify if the blood samples will be collected ad hoc for the study
13. It is not clear why the genetic analysis could show incidental findings: are they expression studies? Are there studies on germinal genes?
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”
15. Add that in case of withdrawal biological samples will be destroyed
16. Explain where the biological analyses will be performed
17. Add the option “non volere partecipare alla sperimentazione”

**Sponsor response:**

First consideration: Thank you for your comment, we amended the sentence, both in consent for minor and parents. Second Consideration: Thank you for your comment, we amended the sentence, both in consent for minor and parents. Consideration: 1. 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 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. 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. we corrected the typo. Consideration: 5. Yes, they are expression studies of genes mentioned in the secondary endpoints. Consideration: 6. we specified that the analysis for genes expression will be performed at the site. Consideration: 7. we corrected the typo. Consideration: 8. 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. “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. 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. we removed the term “ trattamento comparativo” . Consideration 12. we specified that the biological samples “saranno prelevati e utilizzati ai fini della sperimentazioni”. Consideration: 13. they are expression studies of genes mentioned in the secondary endpoints, the reference to incidental findings has been removed. Consideration: 14. we removed these options. Consideration: 15. we added this option in section “ il consenso è definitivo?”. Consideration: 16. we added a sentence to clarify that the biological analyses will be performed at site. Consideration: 17. we added this option in the consent form.

**Consideration number:**

2

**Application section parts**

Part II - Italy

**Application section and document:**

Compliance with national requirements on Data Protection

**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:**

3

**Application section parts**

Part II - Italy

**Application section and document:**

Proof of insurance

**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:**

4

**Application section parts**

Part II - Italy

**Application section and document:**

Suitability of the investigator

**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:**

5

**Application section parts**

Part II - Italy

**Application section and document:**

Subject information and informed consent form

**Consideration:**

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

**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.

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.

Delete: "amministratore di sostegno".

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.

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

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

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 patient about the possible transfer of the biological sample
4. Revise the term “Dimetyl fumarato” in “Dimetil fumarato”
5. Add the information about the study of the other genes: expression studies?
6. Add the information about the place where the genetic analyses will be performed
7. Revise the term “vista “BASALE”” in “visita”
8. Explain what means “randomizzazione”
9. Explain what means “test di funzionalità cardiopolmonare and test per valutare la reazione dei vasi sanguigni (FMD)”
10. Explain what is “placebo”
11. Remove the term “trattamento comparativo” in the phrase “trattamento conservativo/placebo”
12. Clarify if the blood samples will be collected ad hoc for the study
13. It is not clear why the genetic analysis could show incidental findings: are they expression studies? Are there studies on germinal genes?
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”
15. Add that in case of withdrawal biological samples will be destroyed
16. Explain where the biological analyses will be performed
17. Add the option “non volere partecipare alla sperimentazione”
18. Change the phrases “avrà la possibilità di sottoporsi” in “sottoporti”; “Lei ed altre persone” in “tu ed altre”

#### **Sponsor response:**

First Consideration: Thank you for your comment, we amended the sentence, both in consent for minor and parents. Second Consideration: We specified that the insurance deductible will not be paid by the patient in the parents and adults consent, where the insurance is described. Third Consideration: We deleted “amministratore di sostegno” in the parents consent, where is mentioned. Fourth Consideration: We deleted “the sentence” in the parents consent, where it is present. Consideration 1: 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 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: 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: we corrected the typo. Consideration 5: Yes, they are expression studies of genes mentioned in the secondary endpoints. Consideration 6: we specified that the analysis for genes expression will be performed at the site. Consideration 7: we corrected the typo. Consideration: 8. “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: “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: “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: we removed the term “trattamento comparativo” in the Parents consent, where it was mentioned. Consideration 12: 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: they are expression studies of genes mentioned in the secondary endpoints, the reference to incidental findings has been removed. Consideration 14: we removed these options. Consideration 15: we added this case in section “E se ad un certo punto volessi ritirarmi dalla sperimentazione?”. Consideration 16: in section Trattamento dei campioni biologici we added a sentence to clarify that the biological analyses will be performed at site. Consideration 17: we added this option in the consent form. Consideration 18: we changed the phrases.

**Consideration number:**

6

**Application section parts**

Part II - Italy

**Application section and document:**

Subject information and informed consent form

**Consideration:**

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:**

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
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
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 patient about the possible transfer of the biological sample
4. Revise the term “Dimetyl fumarato” in “Dimetil fumarato”
5. Add the information about the study of the other genes: expression studies?
6. Add the information about the place where the genetic analyses will be performed
7. Revise the term “vista BASALE” in “visita”
8. Explain what means “randomizzazione”
9. Explain what means “test di funzionalità cardiopolmonare and test per valutare la reazione dei vasi sanguigni (FMD)”
10. Explain what is “placebo”
11. Remove the term “trattamento comparativo” in the phrase “trattamento conservativo/placebo”
12. Clarify if the blood samples will be collected ad hoc for the study
13. It is not clear why the genetic analysis could show incidental findings: are they expression studies? Are there studies on germinal genes?
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”

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

16. Explain where the biological analyses will be performed

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

**Sponsor response:**

Consideration: 1. 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 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. 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. we corrected the typo. Consideration: 5. Yes, they are expression studies of genes mentioned in the secondary endpoints. Consideration: 6. we specified that the analysis for genes expression will be performed at the site. Consideration: 7. we corrected the typo. Consideration: 8. 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. “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. 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. we removed the term “trattamento comparativo”. Consideration 12. in section 10 we specified that the biological samples “saranno prelevati e utilizzati ai fini della sperimentazioni”. Consideration: 13. they are expression studies of genes mentioned in the secondary endpoints, the reference to incidental findings has been removed. Consideration: 14. we removed these options. Consideration: 15. we added this option in section “il consenso è definitivo?”. Consideration: 16. we added a sentence to clarify that the biological analyses will be performed at site. Consideration: 17. we added this option in the consent form.

**Consideration number:**

7

**Application section parts**

Part II - Italy

**Application section and document:**

Subject information and informed consent form

**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? Will a specific consent

In the document:

INFORMATIVA SUL TRATTAMENTO DEI DATI PERSONALI ANCHE PARTICOLARI: PAZIENTI ADULTI  
INFORMATIVA SUL TRATTAMENTO DEI DATI PERSONALI ANCHE PARTICOLARI PER IL/I GENITORE/I O  
TUTORE LEGALE  
INFORMATIVA SUL TRATTAMENTO DEI DATI PERSONALI ANCHE PARTICOLARI: PAZIENTI MINORI

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; 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; 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)”.

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.”

Delete “e all’ulteriore utilizzo”

**Sponsor response:**

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

Second Consideration:

- “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

## - Requests for information

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