TELETHON GRANT PROJECTS, CALL FOR APPLICATIONS, YEAR 2010

TELETHON REVIEW REPORT

Project number:	**GGP10208**
Applicant's name:	**Gianluigi Forloni**
Host Institution:	**Dipartimento di Neuroscienze, Istituto di Ricerche Farmacologiche "Mario Negri", Milano**
Project title:	**Fatal familial insomnia: preventive treatment with doxycycline of at risk individuals**

GENERAL REMARKS

This year Telethon accepted 229 grant applications. Each application was reviewed in accordance to the policies and procedures of Telethon.

During the initial triage step, each project was evaluated by three members of the Telethon Scientific Committee and received an average score with no written comments.

The bottom 30,1 per cent of all applications (69 out of 229) was excluded from further competition by triage, and will not therefore be receiving any scientific feedback.

The 160 projects that passed the triage phase were then evaluated by *ad hoc* external reviewers and by members of the Scientific Committee (internal reviewers). Written comments were requested at this stage from both external and internal reviewers, and are now being relayed back to the applicants.

A score between 1 and 5 (1 = very poor, 5 = outstanding) was assigned to each project's scientific merit by the internal referees only. During the Scientific Committee meeting, those applications with an average score for scientific merit equal to or lower than 3.7 were not further discussed, unless one score was equal to or higher than 4. This year 78 out of 160 applications were not discussed. All other 82 applications, instead, went on to a thorough plenary discussion.

Each discussed project received three scores, namely one for scientific merit, one for relevance to Telethon and one for proximity to cure, which accounted for 85%, 5% and 10% of the final score respectively.

This scoring mechanism allows the Telethon Scientific Committee to select among projects with similar scientific merit and reward those that are highly relevant and/or possess high therapeutic potential, in line with Telethon's mission.

Results are now being communicated as a ranking in a final, merit-based list only to those applications that were discussed during the Scientific Committee meeting. This year Telethon has funded 40 projects.

The present feedback includes the summary of the comments made by the Scientific Committee members during the plenary discussion, if any took place, together with the anonymous written comments of the single referees.

Although Telethon is willing to relay the views of its referees, it is not prepared to discuss the individual reviewer's opinions. If you have any questions about Telethon policy and procedures, please feel free to contact us.

SUMMARY OF THE DISCUSSION OF THE TELETHON SCIENTIFIC COMMITTEE

The reviewers were extremely interested in this proposal, which is addressing a highly rare and severe genetic disease. The possibility to perform clinical research involving this large genetically well characterized FFA family was considered remarkable and, based on the importance of a clinical trial to test a treatment which could prevent the development of symptoms, the proposal was unanimously approved for funding.

It has to be noted, however, that several issues were highlighted that should be addressed by the applicants before funding is released. In particular, the reviewers were not fully convinced that the study proposed to verify the efficacy of doxycycline is properly designed and likely to produce valuable data. The major concerns were that this is not a randomized placebo control study and that it relies on historical data instead of on recent natural history data collected in a prospective way.

More specifically, the following critical issues were discussed and recommendations given accordingly:

Design of the study:

1. Lack of a "real" placebo controlled group. Try to design the best possible protocol keeping into consideration the concerns highlighted by the reviewers in their written comments: i.e. evaluate the possibility to run a RCT with proper controls; perform less measures but collect them more often;
2. Lack of consistent natural history data. Before starting the treatment, address the need for more natural history data that, for instance, may allow establishing more precisely the range of age of onset. The validity of historical controls is questionable given possible changes in management and standard of care that affect natural history; evaluate the possibility to run a 1 or 2 year observational prospective study to collect natural history data;
3. Power of the study. Try to connect with other clinical groups following similar families to share data on natural history and/or to verify the possibility to involve them in a (parallel) doxycycline trial.

Management:

1. The Coordinator of this project should be a clinician who follows this group of subjects;
2. Schedule milestones to verify first the progress in the planning of the trial, then the subject's enrollment and follow up;
3. Set up a steering committee with external experts in support to the design of the trial and for monitoring milestones;
4. Set up a Data Safety Monitoring Board.

Budget issues:

1. What is missing here is a realistic estimation of the overall cost of the trial, with identification of start-up costs and cost for management of the trial, particularly for:
   - purchasing of the drug and placebo (who is producing and supplying the placebo?)
   - management activities
   - patient-related costs for personnel doing the clinical evaluation;
   - realistic estimation of other personnel (geneticist, biostatistician, etc.) time and costs

   Define the budget based on the approved amount;
2. How is the recruitment of funds envisaged for the continuation of the study after the first 3 years? Indicate how additional money to cover the next 7 year's period will be sought.

A meeting between the Principal Investigators and the Telethon scientific office should take place as soon as possible in order to address the above issues.

Following the discussion, and on the basis of the above-mentioned criteria, the review panel voted that this application would be funded. In the final scoring, the project ranked at the 3rd position.

The referees' written comments are reported below. Telethon hopes the applicant will benefit from the critical and constructive evaluation of the project.

BUDGET

The approved budget is: € 237,200.

Please note that the budget was cut to reflect both the consensus reached during the discussion and the application guidelines. Overall, the budget was considered inflated for the 3 years project and not well justified.

The budget details should be redefined together with the staff of the scientific office with better allocation of start up and follow-up costs. An overall estimation of the 10 year study should be attempted with indication of the plans for scouting of additional money to cover the next 7 year's period.

DESCRIPTION OF THE PROPOSED PROJECT

The investigators propose a safety and efficacy study of doxycycline (DOXY) in subjects at genetic risk to develop fatal familial insomnia (FFI), an ultra-rare, inherited disease related to Creutzfeld-Jakob disease and other transmissible spongiform encephalopathies (TSE). FFI has its onset in adulthood, and causes a fulminant neurologic decline and rapid demise, often within a year of onset. No therapy is proven to delay onset or slow progression. DOXY has shown benefit in model systems of TSE, and preliminary results from human clinical studies in TSE patients suggest a survival advantage in treated individuals compared with historical controls. Single-blind mutation analysis on 85 members of a large Italian FFI family has identified 22 individuals with the disease-causing mutation, 19 of whom have a polymorphism that confers a more severe phenotype. Eleven of these 19 patients fall into the age range assessed as likely to have disease onset within 10 years, based on a historical control. These 11 individuals, along with 11 gene negatives from the same family, comprise the proposed primary study cohort. Additional subjects will be recruited as they move into the target age range. The proposal is for a single-blind, interventional study using an historical control. A placebo will be employed, given only to the gene negative group. A single dose of DOXY, 100 mg per day, will be assessed. Safety measures will include adverse event tracking every 2 months, and clinical laboratory studies every 6 months. Efficacy will be assessed every 2 yrs via clinical measures employed with the presumed goal of detecting disease onset. These will include physical and neurologic examination, MRI imaging of the brain, cognitive testing, EEG polysomnography, actigraphy, and evaluation of autonomic and neuroendocrine function. Data will be entered into a central relational database. The treatment will be deemed effective if 3 or fewer subjects develop manifest disease in 10 years.

WRITTEN REVIEWS

Reviewer 1

Dr. Forloni requests 3 years of funding for a clinical trial in pre-symptomatic people from a pedigree in the Treviso region affected by fatal familial insomnia (FFI). They propose to offer to potential carriers between ages 41 and 52 years who are potential carriers the opportunity to enter into a clinical trial of doxicycline for the prevention of FFI. The family members at risk have already undergone genetic testing, but do not wish to be informed of the results. In consequence, the trial will include the placebo treatment of non-carriers. The active treatment trial for carriers does not include concurrent controls, but relies on comparison to historical controls.

Significance. The partnership between families and their physicians offers a unique opportunity to enhance the knowledge of the natural history of FFI, and to plan for clinical trials. The disease is devastating and there is no treatment. However, it is doubtful if the trial as planned would answer the question if doxycycline is beneficial in the prevention of FFI in carriers.

Preliminary data. Given the rare nature of the disease, and the long observation period needed for clinical trials, there will be very few opportunities to test potential treatments in trials (1-2 every 20 years under the investigators' protocol). As a result, the investigators should be convinced that the ***best possible drug at the best possible dose*** is chosen before starting a long-term trial.

Consider strengthening the pre-clinical data: (1) Is doxycycline is the best drug in its class with regards to its effect on fibrillation? (2) Consider replicating the animal study in scrapie in a randomized, controlled, blinded and adequately powered animal trial. (3) Consider dose-ranging *in vitro* and *in vivo* (animals) to inform dose selection. (4) Include a biomarker evaluation in the animal studies (if feasible assess measures of fibrillation in vivo or pathologically after euthanasia).

For the same reasons stated, consider ***strengthening the clinical preliminary data*** on Creutzfeld Jacob Disease (CJD): (1) Comparing survival between treated and untreated may be confounded by a time effect. Due to medical progress, the natural history of any disease is a moving target. Therefore, consider dichotomizing available data on untreated CJD patients at the median year of incidence (based on the range of year for which incident data are included). Then compare Kaplan Meier plots between the earlier and later cohort. (2) Consider a center effect as possible confounder. Therefore, compare German treated vs. untreated and Italian treated vs. untreated only, but not between centers. (3) In figure 4, were the different codon 129 genotypes approximately evenly distributed between an earlier and later cohort by year of incidence?

Regarding the FFI carrier data: Consider additional genetic investigations in the outlier who remains an asymptomatic carrier at age 81 years.

Appropriateness of methods.

Trial Methodology: Clearly state the primary outcome and further develop power calculations. We commend the investigators for mentioning in the proposal the intent to share outcome measure data with other centers. It would be helpful if the authors stated specifically who they could potentially collaborate with, how many patients their collaborators would have access to, and what specific plan for data standardization and data sharing they propose.

Conducting a trial without concurrent placebo controls not only carries the risk of falsely concluding that doxycycline works under the scenario that the natural history has improved, but the doxycycline is ineffective. Conducting a trial without concurrent placebo controls also deprives the field of the unique opportunity to collect prospective, comprehensive true natural history data (untreated) using a battery of outcomes including neuroimaging, autonomic testing, and clinical measures. Conducting a trial without concurring placebo controls also carries the risk that one would not be able to detect the possibility that doxycycline is harmful. We recommend a one-year interval between visits because pre-clinical changes preceding disease onset and early clinical changes may be missed if they occur in the middle of this relatively large interval. Consider using a battery of sensitive neuropsychological measures as additional clinical outcomes, including for example measures of depression, behavior, language, visual and spatial memory, and executive function.

We recommend that the applicants consider a three year natural history study with at least annual comprehensive measurements of clinical and laboratory outcomes. It will be important to include the older subjects early on. In parallel to the natural history study that should be started soon, we recommend that the investigators develop a revised trial plan based on the Telethon review and on additional expert input they may choose to obtain. The revised plan should include a concurrent placebo control group. Can additional participants be identified through cooperation with other centers (perhaps using parallel studies under one protocol)? A treatment trial should be double-blinded.

Regarding the safety monitoring plan: Perform pregnancy test on women before entry into the trial, and make sure women of childbearing age use two methods of birth control while participating. Perform metabolic laboratory testing and exclude patients with liver and kidney disease. During the trial, regularly monitor kidney and liver function, early on with greater frequency (e.g at month 1,3,6 etc.). In addition to the relatively infrequent visits for efficacy measurements, there would need to be interval study visits for safety and compliance. Establish an independent data and safety monitoring board to review serious adverse events and to annually review efficacy outcomes by group while maintaining the double blind of the investigators. The applicants will need approval by the local ethics board and depending on local regulations may have to submit to other regulatory bodies such as the Italian agency overseeing the approval of experimental medications for use in protocols.

Ethical considerations: Performing a trial that is unlikely to yield clear answers is problematic. If doxycycline prevented disease onset in all cases, then even an uncontrolled trial would be convincing. For any more modest effect size, a concurrently controlled trial would be preferable. The acceptance among families to engage in a placebo controlled trial may be increased by further information and partnership. The physicians could point out the following: If an individual takes an unproven medication in the hope of personal benefit, there always remains the risk that the unproven medication is not only ineffective, but harmful. Examples include a trial of

minocycline in ALS (Gordon, Lancet, 2007) in which the minocycline group showed more rapid disease progression than the placebo group. If all at risk carriers just took an unproven medication, then the question as to whether the drug helps cannot be answered for families at risk. By participating in a clinical trial, an at risk carrier can engage in the altruistic act of helping their family and others to get much needed answers about FFI. A well designed clinical trial can be a success for those affected regardless of its outcome. While everyone hopes for a positive outcome, even a negative trial can benefit affected families if it provides much needed information on the natural history and outcome measures (biological and clinical) that will set the stage for a next trial. The trial should include clear a priori stopping rules for futility. It will be important that the investigators, physicians, and patients maintain equipoise regarding the study drug.

Applicants: The principal investigator should be a clinician. The team would benefit from the advice of a clinical trial expert and a statistician.

Budget: The investigators should submit a revised budget for the natural history study. It is hoped that many of the safety and clinical measures would not have to be covered by research funding. Also, the investigator time could be reduced because of the relatively small number of patients and the relatively infrequent visits. For a clinical trial, the investigators should provide a budget that covers the entire project from start up to recruitment period and follow-up.

Reviewer 2

This proposal describes a clinical trial of doxycycline in familial fatal insomnia. The work derives from a strong interest in FFI by the investigator group and access to a large Italian kindred with numerous 'at risk' individuals. The burden of disease is high. The rationale for use of doxy is its capacity to interfere with pathologic prion aggregate formation in vitro and now in vivo in other forms of prion disease (CJD). The work also will generate critical natural history data to both enable more robust outcome analyses and strengthen clinical trial design for future therapeutics. This is an ultra-rare monogenic disorder and special consideration must be given to statistical power and study design in view of this. The standard requirements for a robust clinical trial are reconsidered in light of the inherent limitations to studying an ultra-rare disorder.

The significance of the proposed work is high and the originality also is high. Few groups could develop the trial, as proposed; the investigator group is uniquely positioned to perform the work and the proximity to a single large kindred with sufficient numbers of 'at risk' members creates a singular opportunity. The choice of doxy is adequately justified and is a relatively low toxicity choice, especially given the high disease burden. The preliminary results are compelling. Feasibility is well-documented. The only issue around feasibility is that the trial is justifiably a 10 year timeline and the funding request is for 3 years. If Telethon elects to fund this trial, a commitment to fund the full study should be explored, given appropriate documentation of meeting milestones and generating the necessary work products. This proposal is highly relevant to Telethon and closely proximate to a cure. The combination of all of these factors creates very high enthusiasm for this proposal.

Comments on Applicant: The investigator group is outstanding to perform the work as proposed. They are uniquely positioned worldwide to complete a clinical trial in FFI, and this trial is likely to provide meaningful data on doxy and related therapies in FFI and other prion diseases.

Comments on Budget Allocation: Salary for a full-time neurologist by Partner 2 is not well justified and seems excessive. Otherwise, the budget is appropriate for 3 years of what is proposed to be a 10 year study. A commitment on the part of Telethon to support the ongoing study for the full 10 years should be explored. This is a major consideration in the support of this project. Realistic milestones should be established with tangible work products expected at key steps during the 10 year trial. With such assurances, Telethon could justify a longer term commitment of funding to this trial, which represents an exceptional opportunity and one that is well-aligned with Telethon priorities.

Overall evaluation

This trial represents an exceptional opportunity to advance treatments and define natural history in prion disorders. The proposal is aligned with Telethon priorities and is uniquely suited to the investigators and the Italian kindred described. The investigator group proximity and connection to a large kindred with sufficient numbers of study participants high burden of disease with low toxicity of putative therapeutic natural history data to be generated is clearly a strength of the project.

Reviewer 3

The study aims to use single blind, "placebo controlled", prospective approach to try to clarify whether the extant antibiotic doxycycline, with a clearly established safety/toxicity profile for human use, has therapeutic efficacy in human prion disease; specifically the genetic form of human prion disease Fatal Familial Insomnia. The applicants are in a relatively unique position of having direct access to a very large, well characterized family affected by this disorder, with many family members, including both pre-symptomatic non-mutation carriers and non-carriers, having agreed to participate in this study.

The study is of potentially great significance. It is well appreciated that once symptoms begin in most neurodegenerative diseases, underlying neuropathology is generally well advanced militating against the success of therapeutic intervention at that stage. By utilising pre-symptomatic, mutation carriers in a disorder with high penetrance, the study has a rare opportunity to offer the best chance for treatment success. Fortunately, the large size of the pedigree and the willingness of family members to participate engender the study with a high likelihood of statistically valid outcomes. The protocol and methods described are entirely feasible and the preliminary results clearly justify the study.

Some reservations I have are:1) why have the applicants not included a placebo treated group of pre-symptomatic mutation carriers?; 2) why has PET imaging not been included in the baseline and monitoring assessments, as abnormalities in the thalamus using this technique have been reported to reliably indicate imminent symptom onset?; 3) given the study is planned for at least 10 years to achieve a meaningful outcome but the funding is only for 3 years, there are concerns that the study may be successfully initiated but not completed and 4) although an interesting and important group of patients, FFI is a rare genetic form of a rare group of diseases; there is a real likelihood that treatment may not be efficacious in the more common forms of disease such as sporadic Creutzfeldt-Jakob disease.

Comments on Applicant: The applicants have established track records and appropriate skills for a study of this type.

Comments on Budget Allocation: The only reservations I have are in relation to staffing and salaries, which appear excessive. Firstly, the study size is very small. Consequently, why for example is a full-time (100%) clinical pharmacologist required by the coordinator for three years? Further, why are three neurologists (equating to a total of 35% of full-time) required for around 30 patients to deliver the neurological examinations? If I have understood the study design, it appears there will be a relatively busy first year enrolling study participants (who have already agreed in principle) and performing the comprehensive baseline battery but thereafter lengthy intervals between many of the follow-up assessments and investigations; however, the budget shows steady salary requirements over the three years of the study, which is therefore difficult to understand.

Overall evaluation

Strengths: Applicants have proven track records and appropriate skills to perform the study. The study design offers an optimal opportunity for assessing therapeutic efficacy. The study participants are ideal for the study and have already agreed in principle to participate in sufficient numbers to allow a likely statistically valid outcome.

Weaknesses: Study design not including placebo treated pre-symptomatic mutation carriers. Funding only available for 3 years for a study intended to span 10 years. Potentially, results may not be generalizable to more common forms of human prion disease such sporadic Creutzfeldt-Jakob disease.

Reviewer 4

This proposal is on a study on preclinical treatment with doxycycline (DOXY) in subjects with a genetic risk to develop fatal familial insomnia (FFI). FFI is a rare genetic neurodegenerative disease, which is linked to the aspartic acid to asparagine mutation at codon 178 of the prion protein. The applicants have identified 85 members of large FFI family, who were genotyped for the D178N, 22 of them were tested positive. The age range of 50−55 years is associated with highest risk to develop FFI. Since the penetrance is very high and the possibility to cure the disease after the clinical onset is remote, the applicants propose a preventive treatment with DOXY. The potential efficacy of DOXY in prion diseases derived from experimental investigations and two clinical observational studies in Italy and Germany with positive effects on survival and negligible side effects in sporadic CJD, another prion disease. They plan to treat 11 carriers and 11 non-carriers with 100 mg daily dose of doxycyclin. This blind application is chosen because individuals participating to the study should remain blind for both, treatment and their genetic condition. Before starting the treatment and every second year afterward all the individuals will be clinically examined, a ten years observation period is planned. During the study, 24-h hour EEG polysomnography, endocrinological parameters, neurological evaluation, MRI, neuropsychological assessment will be regularly performed. The efficacy of the preventive treatment will be evaluated on the percentage of the affected subjects after ten years, according to the statistical analysis if no more than three individuals will become ill within the ten years, the treatment can be considered active to prevent FFI.

Significance: Familial prion diseases, which include 10−15% of CJD cases, GSS and FFI, display autosomal dominant inheritance and are linked to insertional and point mutations in the PrP gene (PRNP), on chromosome 20. FFI is associated with a point mutation (GAC−AAC) in the 178 codon of PRPN. At present, at least 30 FFI pedigrees are known from several countries all over the world. The age between 50 to 55 years bears the maximal risk to develop the disease. The applicants propose a preventive treatment with doxycycline (DOXY) in carriers with a range of age between 42 and 52 years. The major goal is to develop a rationale approach and the adequate conditions to interfere with the development of FFI in a genetic risk population. This is a highly relevant proposal since treatment at the onset of clinical signs of a prion disease can only result in a prolongation of the pathological condition, whereas here a potential preventive effect can be expected.

Originality of science: The aims of this study are original and innovative. To the knowledge of the reviewer, no similar project is underway in any other country in Europe or elsewhere. This is a unique opportunity to study an effect of a preventive treatment in a devastating neurological condition. The study could be a prototype of similar preventive investigations in other genetic neurodegenerative diseases.

Appropriateness of the design: The study design is well developed; the methods are sound and appropriate to the aims of the project. Because a huge amount of preparatory work has been performed already before, the study can start without any delay.

Preliminary results: 85 members of a large FFI family consented to be genotyped for the D178N mutation and 22 of them resulted to carry the mutation. There were 11 subjects with a range of age between 41 and 52 year. These 11 individuals could receive treatment with doxycyclin for least ten years. The non−carriers in the same range of age will receive a placebo, and will be subjected to the same clinical and instrumental analyses as the DOXY−treated group. In this way the individuals participating to the study will remain blind for both the treatment and their genetic condition. The rationale for this study originates from experimental but also clinical investigations, which demonstrated an effect of daily treatment with DOXY 100mg/die as compassionate treatment on sporadic CJD. The Kaplar−Meyer survival curves showed a significant change between treated and non treated subjects, both the medians and the means of the values of survival time were doubled.

Feasibility/Safety: Doxycyclin is a well-known drug with a low side effects profile and has been used for long-term treatment in other conditions. In terms of safety, the administration of the drug is likely to be safe even for such a long time period.

Relevance to Telethon: A priority of Telethon is to support studies on genetic diseases that are neglected by major public and industrial funding. Thus, such a study as proposed here is completely within the scope of Telethon objectives. The study offers a unique opportunity to test in a controlled manner the efficacy of doxycycline as preventive treatment in FFI. The adoption of preventive treatment in genetic risk population is urgently needed.

Proximity to Cure: The preventive treatment with doxycycline of individuals with genetic risk to develop FFI is an advanced approach to overcome the main problem associated to the cure of neurodegenerative disorders constituted by the timing of treatment. Because the neurodegenerative process is already advanced at the clinical onset of the disease, in the genetic disorders the early exposure to a potential drug is the only solution to delay or even prevent disease onset. Since doxycyclin well known drug with low side effects and known side effects in long-term application, the application of this drug to a "population at risk" is the only logical consequence. In the genetic disorders the early exposure to a potential drug is the only solution to delay or even prevent disease onset. Since doxycyclin well known drug with low side effects and known side effects in long-term application, the application of this drug to a "population at risk" is the only logical consequence.

Comments on Applicant: All applicants have a long-standing expertise in the area and are definitely highly qualified to perform such a study. In addition, experiences on a previous and running trial on doxycyclin in sporadic CJD will be of great help to perform this work.

Comments on Budget Allocation: The budget is very reasonable considering the complexity of the work which is planned here. A big advantage is that a high amount of preparatory work has been already done, such as selection of the patients, genotyping, data set up, definition of the protocol. Thus, the study can start immediately without many delays.

Overall evaluation
Strengths: This is a very reasonable study which aims to evaluate efficacy of a preventive treatment with doxycycline in D178N-128m mutation carriers. It definitely could be a prototype of similar preventive investigations in other genetic neurodegenerative diseases.
Weaknesses: The only weakness is explained by the nature of the disease- low numbers of patients will be included and a classical double blind placebo controlled trial is not possible by the nature of the disease. However, data obtained should be compared with "historical" data which are available on FFI.
Final considerations: This study should definitely be performed.

Reviewer 5

This cohort is extremely valuable and represents an extraordinary opportunity to further our understanding of FFI and other spongiform encephalopathies. The group's success in gaining the trust and collaboration of this large family in the proposed project is remarkable. The study's single-blind, single dummy design is a worthy attempt to guarantee gene carriers access to active treatment while protecting gene negative subjects from harm from the same treatment. Further, the design serves to protect all participants from harm from inadvertent release of genetic carrier status information. The proposal's goals are relevant to Telethon's objectives, as it is directed towards disease-modifying therapy of a monogenic disease.

However, the proposal has some flaws. Most significantly, the study seems to be trying to capture natural history data while simultaneously trying to alter it with an intervention. The proposed myriad of clinical assessments will likely be very valuable in deriving the natural history of the disease and in identifying markers of disease onset and progression. But the data will only be useful as such if it is obtained as natural history, not altered by an intervention. Also, whether done within an observational or interventional study, evaluations may need to be done more frequently as patients approach the age of onset, given that the vast majority of patients die within two years of diagnosis. It may be appropriate to consider a more targeted array of studies administered at shorter

intervals and supported by a stronger rationale. The support and collaboration of consultants with specific expertise might be considered. In order to assess the efficacy of an intervention, it must be compared to some sort of control. Although the proposal describes a placebo group, there is not really a true placebo control: there is no randomization but rather a single-blind assignment of gene negatives to dummy treatment and gene positives to active treatment. Thus while the "placebo" group will provide an important ethical safeguard, and control data for the safety and tolerability outcomes, it will not function as a control group for the efficacy outcomes. Rather, the study relies heavily on historical controls as a comparison group for the efficacy outcomes. This is a common and sometimes acceptable solution to the problem of very small numbers of potential study participants in rare disorders; however, the historical control must be a true comparison to overcome the shortcomings of this approach. Here, the historical controls mentioned are for CJD or all TSEs, and the justification in the proposal is weak for these cohorts being representative of FFI (though they may be). The one FFI historical control cohort is represented by Figures 5 and 6, but the figures and the accompanying text do not provide enough information to assess how robust a control the cohort really is. A particular concern is how fundamentally dependent the study design is on the retrospective assessment of age of onset from the historical control: if this differs from the prospective assessment of age of onset by a few years, DOXY may be rejected as ineffective when it may in fact be effective but just started too late (a Type II error). The Huntington disease experience suggests that there may be many years' discrepancy between age of onset assessed retrospectively and that assessed prospectively. The investigators should provide a justification for a single, rather than double-blind design: is there any reason why an investigator truly blind to the subject genetic status / treatment assignment could not do the clinical assessments? Also, there should be a prospective plan for seeking and obtaining post-mortem pathologic specimens if possible.

Overall evaluation

Strengths: The extraordinary cohort of affected individuals, and the strong commitment and connection of this investigator group to the family.

Weaknesses: The study is trying to capture natural history data while simultaneously trying to alter it with an intervention. The proposal's design is highly dependent on natural history age of onset data from historical controls that may not be well matched. If prospectively-derived age of onset differs significantly from the retrospectively-derived control group, the assumptions about power and sample size may be false.

Final considerations: If an interventional study with a low toxicity agent is now anticipated by the Treviso FFI family, there may be limited enthusiasm for proposing an observational study as a preliminary step: individuals may seek to simply take the agent as an open-label agent if there is no trial. But a carefully-designed and executed observational study, even over just 1-2 years, may be sufficient to derive the natural history if both cross-sectional and longitudinal data is captured across the spectrum of disease. This would allow for a more robustly-designed interventional study within a relatively short time.