# Report of the Meeting of European Friedreich's ataxia (FRDA) clinical network

Friday 5th June 2009, nH Jolly Ligure Hotel, Turin, Italy

With the contribution of

## Purpose of the meeting

This meeting was organised by GoFAR with scientific input from Professor Massimo Pandolfo, with the purpose of bringing together the European Friedreich's ataxia clinical network of researchers to discuss the forthcoming clinical trials of HDAC inhibitors. The meeting was strengthened by having a representative from Repligen, the US pharmaceutical company who is the process of developing an HDAC inhibitor drug to be trialled in FRDA. Representatives from European patient groups from France, Spain, Italy, UK and Ireland were also present to express their support of such trials.
The meeting focused on general guidance as to Repligen clinical HDACì development plans and how Repligen can engage with European based centres.
It was also a timely opportunity for the European clinical network of researchers to get together to discuss trial design, to hear from developments in treatment options, and to put forward the Centres of excellence in Europe where trials could take place.

## Outcomes of the meeting

### Centres of excellence

There are at least ten Centres of excellence in Europe with clinical and research expertise in Friedreich's ataxia which are in a good position to run trials of HDAC inhibitors. Many of these Centres have been and are involved in running trials in patients with Friedreich's ataxia (for example testing idebenone, EPO, deferiprone).
The European FRDA Clinical Centres represented at this meeting were based at the following countries: Spain (Dr Javier Arpa), Austria (Dr Sylvia Boesch), United Kingdom (Dr Paola Giunti), France (Dr Cecilia Marelli and Dr Alexandra Durr), Italy (Dr Caterina Mariotti), Spain (Dr José Luís Muñoz Blanco), Italy (Professor Antonio Piga), Belgium (Professor Massimo Pandolfo), Germany (Dr Jorg Schultz), Ireland (Dr Raymond Murphy).

**Support from patient organisations**
Patients support groups are keen to co-operate in trials and this was shown in terms of the representation of groups at this meeting, their financial commitment and their willingness to help with recruitment to trials. Patient support groups in most countries have registries of patients and pooling those together from France, Italy, UK and Ireland alone meant they have access to around 1300 patients.

**Repligen's development plans in FRDA**
The Medical Director of Repligen, Dr David Jacoby, illustrated the company's development plans. They aim to start phase I studies with their most promising drug in 6 months. This will be first in healthy volunteers and then in patients with FRDA in January 2010. They then hope to be starting multi-centre phase II studies in two years time. Dr Jacoby expressed his interest in phase II studies taking place both in the US and in Europe, and acknowledged the expertise and collaborative work ongoing in European Clinical Centres. Repligen has a strong commitment to Friedreich's ataxia.

**Development plans regarding a new HDAC inhibitor**
Professor Festenstein (Imperial College, London) presented data on a new compound which increases levels of frataxin in patient cells and in mouse models. This is an HDAC inhibitor which is commercially available, thus fewer safety studies would be needed. He plans to do a proof-of-concept trial in a small number of FRDA patients soon and if successful this would be followed by a multi-centre trial with other European partners after that.

**Discussion on trial design**
Given the imminence of these potential human trials testing HDAC inhibitors, it was timely to discuss trial design. A very useful discussion was held.

a) Endpoints - biomarkers
There was agreement on the importance of measuring frataxin protein and mRNA levels as primary endpoints for proof of concept studies, and as a secondary endpoints for phase II studies.

b) Endpoints - rating scales
There are three potential rating scales that could be used: ICARS, FARS and SARA. All agreed that there are a number of limitations of both ICARS and FARS for use in Friedreich's ataxia, and the time required to complete these is also very long. In general there was much support for the use of SARA. The use of the FRDA specific quality of life rating scale (FAIS) was highligted as a secondary outcome endpoint.

c) Inclusion/ exclusion criteria
Consensus was reached on the usefulness of including both children and adults in trials. Also patients would have to be homozygous for the FRDA mutations. All other standard exclusion criteria (eg: pregnancy) would also be included.

d) Concomitant medications (eg: idebenone)
It was agreed that it would be impossible to prevent participants from taking medications that are approved medications for FRDA at the time of the trial. Thus, if

idebenone was an approved medication it would have to be accepted that patients could take it. The use of CoQ10 was not considered to be a problem, as it did not act in the same disease-modifying way as HDAC inhibitors. Medications which were being taken by patients on a trial basis, such as deferiprone would not be allowed medication for study participants.

e) Study design
For the multi-centre phase II and III, there may be a need to be more imaginative. The standard double-blind placebo controlled design is useful, however, if it becomes difficult to recruit participants to trials, due to the lack of people wanting to be on the placebo arm, it would be possible to do trials in which all patients would eventually be on the treatment arm. There was generally a commitment to look at such novel trial design to satisfy patient aspirations.

f) Interaction with EMEA
The need to be in contact with the EMEA from the beginning was acknowledged, in order to engage them in initial discussions, with regard to orphan drug designation and trial design for subsequent drug approval.

**Funding of trials**
Repligen – The company is committed to taking its FRDA programme forward and hopefully starting human trials soon.

European Commission - Professor Pandolfo informed those present that there is a new call for proposals and all agreed that the criteria seem to fit and there was enthusiasm for submitting a bid. The focus of the new application would be testing HDAC inhibitors. One of the criteria for applying is that the drug being tested has orphan drug designation status.

## Actions

**1) Meeting with EMEA arranged**
Given the timings with the EC funding application a meeting with the EMEA relevant Committee should be held soon. It would be useful for European expert clinicians to attend with Repligen.

**2) Application to EC for FRDA project to be submitted**
Massimo Pandolfo will take the lead in preparing the application (with support from other researchers and, if needed, patient support groups). This proposal would focus on testing human trials of HDAC inhibitors.

## Conclusions

A European FRDA Clinical network is in place, made up of a number of Centres with expertise. There is also commitment from patient support groups across Europe to help in the research effort. At this meeting some preliminary agreements were made in trial design and commitment for doing further preparatory work in order to start HDAC inhibitor trials within the next two years. Repligen is interested in running trials in Europe and recognises the need to enter into discussions with EMEA this year.

There is a need for orphan drug designation status for the drugs to be tested in trials. The European network is committed to continue meeting and to prepare baseline data for Repligen phase II trials. There is also a commitment to submit a large funding bid to the EC incorporating the Repligen drug trial. Similar meetings should be held to discuss unresolved issues in trials.

sponsored