



Pharmacodynamic studies of a histone deacetylase inhibitor in Friedreich's ataxia

Principal Researchers: Professor Richard Festenstein, Imperial College
Department of Medicine

Scientific abstract

Friedreich's ataxia (FRDA) is caused by a GAA repeat expansion in the *Frataxin* gene causing its repression which resembles the archetypal epigenetic phenomenon of Position Effect Variegation and hence can be modulated by chromatin modifiers (Saveliev et al., 2003). We have now confirmed that a similar form of silencing occurs in cells from FRDA patients. Based on these findings histone deacetylase (HDAC) inhibitors which can overcome such silencing have been identified (Festenstein, 2006; Herman et al., 2006). We have extended this result by showing that a classical Class III HDAC inhibitor can relieve silencing in cells from people with Friedreich's ataxia. This HDAC inhibitor has been previously administered to humans with no significant ill effects (Gale et al., 2004). We will perform pharmacodynamic studies on this compound in humans with FRDA to investigate whether we can upregulate Frataxin and if so, to determine an optimum dosing regimen. The drug will be administered orally following a standard drug escalation regimen and blood samples taken to measure Frataxin level and chromatin structure of the Frataxin gene. The end-point of the study is to achieve significant upregulation of Frataxin in people with Friedreich's ataxia providing a potential therapy for this currently untreatable condition.

Lay summary

The aim of this project is to find out whether we can switch on the gene which is largely inactive in Friedreich's ataxia (FA), potentially providing a radical new therapy. We have previously shown, in a project funded by Ataxia UK, that an HDAC inhibitor drug can switch on this gene in cells from patients in the laboratory and can also increase levels of the frataxin protein that is deficient in people with FA. The drug is thought to work by 'opening up' the gene making it accessible to the machinery which switches it on. The drug we are testing has already been shown to be tolerated and safe in humans as it is commercially available for another condition.

In this first pilot trial a small number of people with FA will be given oral doses of an HDAC inhibitor. We will establish what the 'normal' levels of frataxin are in healthy volunteers and carriers of the FA gene. We will gradually increase the dose given to patients until we observe an increase in frataxin levels or until we reach the safety limit. This will be done over a period of a few days for each participant. This study will only tell us if we can increase frataxin levels sufficiently. If successful, further trials will be needed to test whether this drug has an effect on the progression or severity of the condition.



Will you need people to volunteer to take part in this trial?

As this is only a small proof-of principle study we do not currently need any more patients for this study. However, if this pilot trial is successful, a larger trial to test efficacy will be planned, and at that point we will inform Friends of Ataxia UK of the opportunity to take part and would be most grateful for your support.

This project is co-funded with Friedreich's Ataxia Society, Ireland (FASI) and the Association Suisse de l'Ataxie de Friedreich.

For more support or information please contact: Ataxia UK, Lincoln House, Kennington Park, 1 – 3 Brixton Road. London SW9 6DE

Website: www.ataxia.org.uk.

Helpline: 0845 644 0606 Tel: +44 (0)20 7582 1444 Fax: +44 (0)20 7582 9444

Email: helpline@ataxia.org.uk.