CLINICAL STUDY SYNOPSIS: *The pharmacological effects of granulocyte-colony stimulating factor (GCSF) on frataxin expression in patients with Friedreich Ataxia*
EudraCT number: 2017-003084-34; Sponsor's protocol code number: 2823

NAME OF SPONSOR University of Bristol **NAME OF FINISHED PRODUCT** N/A **NAME OF ACTIVE INGREDIENT(S)** Granulocyte-colony stimulating factor			**(FOR NATIONAL AUTHORITY USE ONLY)**
Title of Study	The pharmacological effects of granulocyte-colony stimulating factor (GCSF) on frataxin expression in patients with Friedreich's Ataxia		
Investigator(s)	Alastair Wilkins (PI), University of Bristol, UK		
Study centre(s)	University of Bristol, UK; North Bristol NHS Trust		
Publication	N/A		
Study period	From: 1.6.18 To: 12.04.19	Phase of development	Phase II
Objectives	Primary Objective To determine whether granulocyte-colony stimulating factor (G-CSF) administration to patients with Friedreich's Ataxia (FA) cause elevation in frataxin gene and protein expression in peripheral blood cells. Secondary Objective To determine whether GCSF administration (single course) is safe in patients with FA.		
Methodology	The effect of G-CSF on frataxin expression (and related molecules) was assessed by blood sampling during and after treatment. Participants were assessed clinically to determine whether there were any side effects and using haematological and biochemical blood monitoring.		
Number of patients	Planned: 7 Analysed: 7		
Diagnosis and main criteria for inclusion	Friedreich's Ataxia (FA) Inclusion criteria: Genetic diagnosis of FA; Age of over 18		
Test product, dose and mode of administration	Lenograstim (Granocyte ®) by subcutaneous injection (1.28 million units/kg daily for 5 days)		
Duration of treatment	5 days		
Criteria for evaluation	Efficacy: analysis of frataxin protein and gene expression in peripheral blood mononuclear cells; analysis of related anti-oxidant enzymes in peripheral blood mononuclear cells; frataxin protein and gene expression in platelets. Safety: clinical history and examination; haematological and biochemical screening before, during and after therapy.		
Statistical methods	The maximum peak (P_{max}) value for a change in protein concentration or enzyme activity was calculated using a baseline of Y = 1 [Day 1], considering both positive and negative peaks. The sign test was used to compare P_{max} values to a theoretical median of 1.0		

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SUMMARY CONCLUSIONS

EFFICACY RESULTS

Mean baseline frataxin protein levels in isolated peripheral blood mononuclear cells (MNCs) and platelets of participants with FA were 2.46 pg/µg of protein (range 0.18 – 4.00) and 1.60 pg/µg (range 0.80 – 2.71) respectively. Prolonged increases in frataxin expression were evident following 5 days of G-CSF administration in both MNCs and platelets. Maximal 3.10 and 1.96 mean-fold increases in frataxin expression were observed in MNCs (day 6) and platelets (day 8) respectively, with the lower limit of the standard errors remaining above the null value of 1.0 at all time points. P_{max} values for changes in frataxin expression were positive for all six participants over the duration of the study ($P_{max} \neq 1.00$; $P < 0.05$). In response to G-CSF, the mean-fold change in enzyme activity of aconitase and succinyl dehydrogenase (SDH) rose steadily over the study period with maximal 3.69 (day 15) and 3.04 (day 19) mean-fold changes respectively**.** P_{max} values for changes in both aconitase and SDH activity were positive in five of the six participants, however statistically there was no evidence of changes in aconitase or SDH activity for the study duration ($P_{max} \neq 1.00$; both $P = 0.22$). Reduced activities of cell regulatory proteins: peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α); nuclear respiratory factor 1 (NRF1); and nuclear factor E2-related factor 2 (Nrf2) are associated with frataxin deficiency. The expression of PGC-1α, NRF1 and Nrf2 proteins in isolated peripheral blood MNCs were measured in response to G-CSF administration. Marked, rapid and sustained increases in PGC-1α expression were observed post G-CSF treatment, with a maximal 2.94 mean-fold increase in expression at day 6. Peak Nrf2 expression followed at day 15 with a maximal 1.98 mean-fold increase. For both PGC-1α and Nrf2, the lower limit of standard error for changes in protein expression remained above the null value of 1.0 for the entirety of the study. For changes in both PGC-1α and Nrf2 expression, all 6 participants displayed positive P_{max} values ($P_{max} \neq 1.00$; $P < 0.05$). NRF1 displayed greater heterogeneity in response. There was no evidence of changes in NRF1 expression for the study duration.

SAFETY RESULTS

7 participants with FA were recruited to the study between June 2018 to October 2018. Six participants completed the study; one withdrew following the first dose of G-CSF (day 1) due to nausea. Of the participants completing the study, three reported a single, mild adverse event during the period of G-CSF administration; musculoskeletal pain (predominantly in the legs) (n=2) and mild headache (n=1), all of which were listed in the trial protocol as known side effects and all resolved immediately after cessation of therapy. There were no serious adverse events. Although normal pre-treatment, alkaline phosphatase levels were both elevated and outside normal physiological ranges following G-CSF administration as expected (day 6; $P < 0.05$) but these were not associated with symptoms and resolved spontaneously by day 19. All other parameters were within normal physiological ranges. Full blood count at day 6 showed an appropriate marked rise (approximately 7-fold) in total circulating number of white blood cells in response to G-CSF administration, corresponding with significantly elevated numbers of circulating neutrophils, lymphocytes, monocytes and eosinophils ($P<0.05$).

CONCLUSION

We have shown that G-CSF therapy in participants with FA is safe and leads to significant elevations in frataxin together with improvements in several of the biochemical deficits associated with FA. This study provides proof-of-principle evidence to support an efficacy study of G-CSF administration in FA, using repeated courses over a longer period.

DATE OF THE REPORT: 19.12.19