

## Sanfilippo Clinical Trial

### **A Phase III, Double Blinded, Randomised, Placebo Controlled Clinical Trial of High Dose Oral Genistein Aglycone in Patients with Sanfilippo Syndrome (Mucopolysaccharidosis III A, B and C) - GENiSIS2013.**

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We will soon be recruiting for a phase III, double blinded, randomised, placebo controlled clinical trial of high dose oral genistein aglycone in Sanfilippo diseases (MPSIIIA, B and C). This is funded by the UK society for Mucopolysaccharide Diseases, The National MPS society and the GEM appeal in a grant to Dr Brian Bigger and sponsored by the Central Manchester Universities Hospitals NHS Foundation Trust. We expect to begin recruiting in early 2014, primarily from within the UK.

The trial will be regulated by the UK MHRA, performed at the NIHR/Wellcome Trust Clinical Research facility in Manchester using GMP grade genistein aglycone. The trial will be one year placebo controlled with one year open label extension with robust efficacy and safety endpoints.

The Manchester Group published preclinical data in the mouse model of Sanfilippo disease IIIB (MPSIIIB) showing significant delay in neurodegeneration and behavioural correction following high daily doses of the drug genistein aglycone delivered over a 9 month period (Malinowska et al. 2010).

Genistein is a substrate reduction therapy drug and works by reducing the levels of accumulated HS in the body as well as the brain. It is also an anti-inflammatory agent. Genistein in food supplement form has been tested in several clinical trials for patients with Sanfilippo disease. Most showed no measurable clinical effect, although one trial showed reduction of urine GAGs over a year (de Ruijter et al. 2012). These trials used low daily doses of genistein (up to 10 mg/kg/day) in a supplement form. This is unlikely to reach the brain in sufficient quantity to affect neurological disease.

Genistein in the preclinical study (Malinowska et al. 2010) was synthetically produced and is the pure (aglycone) form of the drug. Genistein can also be purified from soy extract but this is not necessarily the same product, as the naturally occurring form of genistein may not be absorbed as efficiently by the digestive system.

High daily doses of genistein aglycone are more appropriate for Sanfilippo as humans have a higher rate of breakdown of genistein (Glucuronidation) than that of mice. This means that higher oral doses are required to achieve equivalent plasma and thus high brain levels of active drug.

High daily doses of genistein aglycone have been delivered to patients over a one year period in an open label safety study in the USA providing significant safety data on the drug (Kim et al. 2013). In order to establish if genistein aglycone is effective at treating the brain in Sanfilippo disease a placebo controlled clinical trial using high oral doses is required.

### About the Disease

Sanfilippo disease describes four clinically identical diseases (Mucopolysaccharidosis – MPS IIIA, IIIB, IIIC and IIID) caused by a lack of enzymes that break down the long-chain sugar heparan sulphate (HS). HS builds up in all cells of the body but mainly affects the brain.

Children with MPS IIIA and B show hyperactivity and a rapidly deteriorating mental state from 2-4 years of age. This includes loss of speech and dementia, severe behavioural problems and sleep disruption over several years with progressive physical and mental disability, followed by death in their mid-twenties.

MPSIIIC patients differ only from the majority of MPSIIIA and IIIB patients in that disease progression is usually less rapid. However there is a wide phenotypic variability between and within all patient subgroups. There are no treatment options for Sanfilippo.

### About the Manchester Group

The Manchester group handles over 15,000 diagnoses per annum for pediatric metabolic diseases from over 30 countries and see approximately 350 lysosomal disease patients every year. They are a nationally designated centre for lysosomal disease management in the UK, helped write national and international guidelines for management of many lysosomal diseases and contributed to several natural history studies.

They have been involved in over 30 clinical trials, some of which led to licensing of 6 drugs worldwide (of 9 available) for lysosomal storage diseases, including trials for mucopolysaccharide disease (MPS) I, II, IIIA, IVA, VI, Fabry, Pompe and Niemann Pick C. As a result, over 800 lysosomal disease patients now receive treatment in the UK and several thousand worldwide.

Research in the Manchester group has helped to move enzyme treatment into the home, thus improving quality of life for the majority of lysosomal disease patients on enzyme replacement in the UK. It has also broadened the scope of haematopoietic stem cell transplantation for lysosomal disease and reduced mortality, benefiting over 100 patients worldwide. Preclinical treatments in development for lysosomal diseases include high-dose genistein for MPSIII, haematopoietic stem cell gene therapy for MPSIIIA & MPSIIIB, and intracranial gene therapy for MPSIIIC.

The preclinical genistein publication is available for free from PLoS ONE at the following link  
<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0014192>

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