

# **High dose genistein treatment in children with Sanfilippo disease shows no clinically meaningful benefit**

**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 have recently concluded a phase III, double blinded, randomised, placebo controlled clinical trial of high dose oral genistein aglycone in Sanfilippo diseases (MPSIIIA, B and C). This was a collaborative academic trial funded by the UK society for Mucopolysaccharide Diseases, The National MPS society and the GEM appeal in a grant to Professor Brian Bigger and sponsored by the Manchester University NHS Foundation Trust.

The trial was led by Dr Simon Jones at the NIHR Manchester Clinical Research Facility at the Royal Manchester Children's Hospital using GMP grade genistein aglycone.

The aims of the trial were to evaluate the safety and efficacy of high dose genistein aglycone in patients with MPSIIIA, B and C. Patients received 160 mg/kg/day genistein or placebo for one year, followed by a year of open label genistein. Levels of plasma, urine and CSF Heparan sulphate (HS), as well as urine GAGs were measured at baseline, 1 and 2 years, together with a range of neuropsychological tests and actigraphy.

Twenty one patients were enrolled, and two withdrew during the study. There were no significant adverse safety findings in the study.

No measurable clinical benefit was demonstrated from the neuropsychological tests performed. The change in Developmental Quotient at 12 months (adjusted for baseline) was not significantly different between the genistein and placebo groups.

Although CSF HS at 12 months (adjusted for baseline) was slightly lower in the genistein group, the primary endpoint of a significant reduction in CSF heparan sulphate was not met.

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. 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 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 was unlikely to reach the brain in sufficient quantity to affect neurological disease.

Genistein in the preclinical study (Malinowska et al. 2010) and this clinical trial 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 were delivered to Sanfilippo patients as humans have a higher rate of breakdown of genistein (Glucuronidation) than that of mice, and therefore a high oral dose is required to achieve equivalent plasma and thus high brain levels of active drug.

The data from this trial do not support the use of off label high dose genistein aglycone for Sanfilippo disease in children. No further clinical trials with this product are planned.

The researchers and clinicians involved in the trial would like to thank the patients, families and MPS societies for supporting this important work. The team remain committed to undertake further research to improve the care of Sanfilippo Syndrome.