



## Clinical trial results:

### A Phase III, Double Blinded, Randomised, Placebo Controlled Clinical Trial of High Dose Oral Genistein Aglycone in Patients with Sanfilippo Syndrome (Mucopolysaccharidosis III)

#### Summary

EudraCT number	2013-001479-18
Trial protocol	GB
Global end of trial date	30 June 2018

#### Results information

Result version number	v1 (current)
This version publication date	21 May 2020
First version publication date	21 May 2020

#### Trial information

##### Trial identification

Sponsor protocol code	GENiSIS2013
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference: 14/NI/0006, Protocol number: GENiSIS2013

Notes:

##### Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Oxford Road, Manchester, United Kingdom, M13 9WL
Public contact	Lynne Webster, Manchester University NHS Foundation Trust, +44 161 2764125, research.sponsor@mft.nhs.uk
Scientific contact	Lynne Webster, Manchester University NHS Foundation Trust, +44 161 2764125, research.sponsor@mft.nhs.uk

Notes:

##### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	30 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2018
Global end of trial reached?	Yes
Global end of trial date	30 June 2018
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of this trial is to evaluate oral genistein aglycone therapy in patients between 2 and 15 years old with MPS III A, B or C

Protection of trial subjects:

A local anaesthetic (usually a cream) will be used to minimise the discomfort when blood is taken. There is a small risk of infection but every effort will be made to minimise this risk. The amount of blood taken will be carefully monitored to ensure too much blood is not taken.

General anaesthesia: Anaesthesia affects the whole body, including the brain, heart, and lungs. The child will be under the supervision of the anaesthesia team from the time the medication is given until the child is again fully awake.

Lumbar puncture: A sample of spinal fluid will be taken by performing a lumbar puncture. After a lumbar puncture, some people will have a headache and there is also the risk of pain at the injection site, meningitis, bleeding, spinal fluid leakage, nerve damage, and paralysis. Every effort will be made to minimise these risks.

If a child has not had genetic testing to confirm their diagnosis of MPS III, this will be offered to them. Learning these results may be useful for the child's health care. The risks of learning genetic test results may include emotional upset and/or family conflicts from learning unknown information about you, your child, your parents or blood relatives. Having the test or the results can be discussed with a genetic counsellor who can help explain the possible risks and benefits of learning this information.

Background therapy:

Although this study is placebo controlled, no treatment will be withheld. After the initial 12 months period all patients will move on to an open label phase where all patients will be given the study drug.

Evidence for comparator: -

Actual start date of recruitment	01 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	14
Adolescents (12-17 years)	7
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

UK only, recruitment period from 01/08/2014 - 31/01/2017.

### Pre-assignment

Screening details:

Genotyping, demographics, medical history

### Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Genistein
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Genistein aglycone
Investigational medicinal product code	500 0500 0
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

160mg/kg per day for maximum duration of 104 weeks (including a 52 week open label treatment period)

<b>Arm title</b>	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

N/A - placebo.

Number of subjects in period 1	Genistein	Placebo
Started	9	12
Completed	9	11
Not completed	0	1
Logistical reasons	-	1

<b>Period 2</b>	
Period 2 title	Placebo controlled phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Data analyst, Subject
<b>Arms</b>	
Are arms mutually exclusive?	Yes
<b>Arm title</b>	Genistein
Arm description: 160mg/kg/day genistein aglycone	
Arm type	Experimental
Investigational medicinal product name	Genistein aglycone
Investigational medicinal product code	500 0500 0
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use
Dosage and administration details: 160mg/kg per day for maximum duration of 104 weeks (including a 52 week open label treatment period)	
<b>Arm title</b>	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use
Dosage and administration details: N/A - placebo.	

Number of subjects in period 2	Genistein	Placebo
Started	9	11
Completed	9	11

**Period 3**

Period 3 title	Open label extension
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Genistein

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Genistein aglycone
Investigational medicinal product code	500 0500 0
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

160mg/kg per day for maximum duration of 104 weeks (including a 52 week open label treatment period)

<b>Arm title</b>	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

N/A - placebo.

<b>Number of subjects in period 3</b>	Genistein	Placebo
Started	9	11
Completed	9	10
Not completed	0	1
Adverse event, non-fatal	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Genistein
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Genistein	Placebo	Total
Number of subjects	9	12	21
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	7.2	5.9	
full range (min-max)	5.1 to 15.9	3.1 to 15.2	-
Gender categorical Units: Subjects			
Female	3	7	10
Male	6	5	11
MPS group Units: Subjects			
IIIA	5	7	12
IIIB	3	1	4
IIIC	1	4	5
CSF HS Units: ng/ml			
arithmetic mean	1632	1499	
standard deviation	± 362	± 284	-
Plasma HS Units: ng/ml			
arithmetic mean	1680	1500	
standard deviation	± 426	± 310	-
Urine HS Units: mg/mmol creatinine			
arithmetic mean	33.2	36.4	
standard deviation	± 28.2	± 25.1	-
Urine GAG			

Units: mg/mmol creatinine arithmetic mean standard deviation	57.9 ± 23.8	66.3 ± 35.2	-
BSID-III DQ Units: Scale arithmetic mean standard deviation	17 ± 10	29 ± 24	-
Beck Depression Inventory Units: Scale arithmetic mean standard deviation	10.9 ± 8.1	14.1 ± 9.1	-
Parents PedsQL Units: Percentage arithmetic mean standard deviation	61.3 ± 14.4	55.8 ± 16.4	-
PedsQL Family Impact Units: Percentage arithmetic mean standard deviation	42.3 ± 14.2	48.8 ± 15.8	-



## End points

### End points reporting groups

Reporting group title	Genistein
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Genistein
Reporting group description: 160mg/kg/day genistein aglycone	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Genistein
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

### Primary: CSF Heparan sulphate

End point title	CSF Heparan sulphate
End point description:	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	Genistein	Placebo	Genistein	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	11	9	11
Units: ng/ml				
arithmetic mean (standard deviation)	1632 (± 362)	1499 (± 284)	1597 (± 373)	1580 (± 303)

End point values	Genistein	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: ng/ml				
arithmetic mean (standard deviation)	1649 (± 468)	1578 (± 403)		

## Statistical analyses

<b>Statistical analysis title</b>	Estimated effect of Genistein
Statistical analysis description:	
% Difference between groups at 12 months, adjusted for baseline	
Comparison groups	Genistein v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	ANCOVA
Parameter estimate	Percentage difference
Point estimate	-5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	4.7

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events will be reported at screening (day -21) baseline (day -21 to -1), and weeks 0, 4, 13, 26, 39, 52, 56, 65, 78, 91, 104 & 108

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	3

### Reporting groups

Reporting group title	Genistein
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Genistein	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	1 / 11 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Gastrostomy tube placement			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Bullous impetigo			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Genistein	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	11 / 11 (100.00%)	
General disorders and administration site conditions			

Febrile illness, unspecified subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	2 / 11 (18.18%) 5	
Emotional Inability subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	3 / 11 (27.27%) 3	
Dental decay subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Dental extractions subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Ingrowing toenail subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1	
Immune system disorders Tonsillectomy and/or adenoidectomy subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 11 (18.18%) 2	
Social circumstances Accidental injuries subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	1 / 11 (9.09%) 1	
Reproductive system and breast disorders Breast tissue development (Tanner stage II) subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 3	0 / 11 (0.00%) 0	
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1	
Respiratory, thoracic and mediastinal disorders			

Upper respiratory tract infections subjects affected / exposed occurrences (all)	8 / 9 (88.89%) 15	8 / 11 (72.73%) 15	
Hay fever subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2	0 / 11 (0.00%) 0	
Sleep disordered breathing subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	0 / 11 (0.00%) 0	
Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Shortness of breath subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Sinusitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1	
Psychiatric disorders Increasing aggressive behaviour subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 11 (9.09%) 1	
Sleep disturbance subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	0 / 11 (0.00%) 0	
Injury, poisoning and procedural complications Needlestick injury subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Stress fracture of foot subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Nervous system disorders New onset seizures / increasing seizure frequency subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 4	1 / 11 (9.09%) 1	

Decreased responsiveness subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Dystonia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Increasing hyperactivity subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Sleep myoclonus subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Vacant episodes subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1	
Ear and labyrinth disorders Deteriorating hearing loss subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Eye disorders Eyelid infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1	
Gastrointestinal disorders Gastroenteritis subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 7	2 / 11 (18.18%) 3	
Vomiting subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	6 / 11 (54.55%) 7	
Constipation subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	0 / 11 (0.00%) 0	

Diarrhoea subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 11 (9.09%) 1	
Hepatobiliary disorders Abnormal liver function tests (not present at baseline) subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	2 / 11 (18.18%) 1	
Skin and subcutaneous tissue disorders Skin infection subjects affected / exposed occurrences (all)  Fungal skin infection subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2  1 / 9 (11.11%) 1	0 / 11 (0.00%) 0  0 / 11 (0.00%) 0	
Renal and urinary disorders Enuresis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1	
Endocrine disorders Abnormal thyroid function tests (not present at baseline) subjects affected / exposed occurrences (all)  Elevated testosterone levels (not present at baseline) subjects affected / exposed occurrences (all)  Precocious puberty subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2  2 / 9 (22.22%) 2  1 / 9 (11.11%) 1	3 / 11 (27.27%) 3  0 / 11 (0.00%) 0  0 / 11 (0.00%) 0	
Musculoskeletal and connective tissue disorders Knee dislocation subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	
Infections and infestations Chicken pox subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0	

Glandular fever			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Infected gastrostomy site			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	
occurrences (all)	1	0	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None.
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Notes: