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

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:

Results analysis stage

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:

General information about the trial

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:

Population of trial subjects

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:

Subjects enrolled per age group	
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
Arm title	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)

Arm title	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 1	Genistein	Placebo
Started	9	12
Completed	9	11
Not completed	0	1
Logistical reasons	-	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	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)

Arm title	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
Arm title	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)

Arm title	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 3	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	57.9	66.3	
standard deviation	± 23.8	± 35.2	-
BSID-III DQ			
Units: Scale			
arithmetic mean	17	29	
standard deviation	± 10	± 24	-
Beck Depression Inventory			
Units: Scale			
arithmetic mean	10.9	14.1	
standard deviation	± 8.1	± 9.1	-
Parents PedsQL			
Units: Percentage			
arithmetic mean	61.3	55.8	
standard deviation	± 14.4	± 16.4	-
PedsQL Family Impact			
Units: Percentage			
arithmetic mean	42.3	48.8	
standard deviation	± 14.2	± 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

Statistical analysis title	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

Dictionary used

Dictionary name	MedDRA
Dictionary version	3

Reporting groups

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

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

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

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

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

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.

Notes: