Clinical trial results:
An international, multicentre, randomised, open-label, no-treatment controlled, parallel group, dose-response study to investigate the effect of once daily nitisinone on 24-hour urinary homogentisic acid excretion in patients with alkaptonuria after 4-weeks treatment.

Summary

EudraCT number	2012-005340-24
Trial protocol	GB
Global end of trial date	13 December 2013

Results information

Result version number	v1 (current)
This version publication date	16 July 2022
First version publication date	16 July 2022
Summary attachment (see zip file)	SONIA 1 Main & Supplementary paper (SONIA 1 Main & Supplementary paper.pdf)

Trial information

Trial identification

Sponsor protocol code	SONIA1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01828463
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Liverpool & Royal Liverpool University Hospital dom
Sponsor organisation address	Prescot St, Liverpool, United Kingdom, L7 8XP
Public contact	Principal Investigator, Royal Liverpool Unversity Hospital (RLUH), 0044 1517062000, lrang@liverpool.ac.uk
Scientific contact	Principal Investigator, Royal Liverpool Unversity Hospital (RLUH), 0044 1517062000, lrang@liverpool.ac.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	10 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 December 2013
Global end of trial reached?	Yes
Global end of trial date	13 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of different doses of once daily nitisinone on 24-hour urinary homogentisic acid excretion (u-HGA24) in patients with alkaptonuria after 4-weeks treatment.

Protection of trial subjects:

Short term study, so no specific protection, warning of ocular toxicity, and to inform study team if such events occured.

Background therapy:

All and any co-coniment medications were allowed, no other background thearpy.

Evidence for comparator:

No treatment (0mg) versus with 1, 2, 4 & 8mg. no comparator medication.

Actual start date of recruitment	25 March 2013
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: 15
Country: Number of subjects enrolled	Slovakia: 25
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	37
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Inclusion criteria
1. Diagnosis of AKU verified by documented elevated urinary homogentisic acid excretion.
2. Age ≥18 years.
3. Willing and able to visit the investigational site for study visits.
4. Signed written informed consent given

Exclusion criteria
The presence of any of the following will exclude a patient from inclusion in the st

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was open label, since it is not feasible to blind a study with HGA-lowering treatment in AKU. One of the cardinal signs of AKU is urine darkening on standing as HGA is oxidised. Patients could therefore easily know whether they were on nitisinone or not. Furthermore, any personnel involved at the investigative sites who were involved in the processing of urine samples would also be able to see this difference.

Arms

Are arms mutually exclusive?	Yes
Arm title	Untreated

Arm description:

No treatment provided

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	1 mg

Arm description:

1mg of nitisinone over 4 weeks

Arm type	Active comparator
Investigational medicinal product name	Nitisinone
Investigational medicinal product code	
Other name	Orfadin
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Suspension - oral
4 mg/mL dosage
1 mg (0.25 mL) Once daily

Arm title	2mg nitisinone

Arm description:

2mg nitisinone daily over 4 weeks

Arm type	Active comparator

Investigational medicinal product name	Nitisinone
Investigational medicinal product code	
Other name	Orfadin
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Suspension - oral
4 mg/mL dosage
2 mg (0.50 mL) Once daily

Arm title	4mg nitisinone

Arm description:

4mg of nitisinone daily over 4 weeks

Arm type	Active comparator
Investigational medicinal product name	Nitisinone
Investigational medicinal product code	
Other name	Orfadin
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Suspension - oral
4 mg/mL dosage
4 mg (1.0 mL) Once daily

Arm title	8mg nitisinone

Arm description:

8mg of nitisinone daily over 4 weeks

Arm type	Active comparator
Investigational medicinal product name	Nitisinone
Investigational medicinal product code	
Other name	Orfadin
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Suspension - oral
4 mg/mL dosage
8 mg (2.0 mL) Once daily

Number of subjects in period 1	Untreated	1 mg	2mg nitisinone
Started	8	8	8
Completed	8	8	8

Number of subjects in period 1	4mg nitisinone	8mg nitisinone
Started	8	8
Completed	8	8

Baseline characteristics

Reporting groups	
Reporting group title	Untreated
Reporting group description:	
No treatment provided	
Reporting group title	1 mg
Reporting group description:	
1mg of nitisinone over 4 weeks	
Reporting group title	2mg nitisinone
Reporting group description:	
2mg nitisinone daily over 4 weeks	
Reporting group title	4mg nitisinone
Reporting group description:	
4mg of nitisinone daily over 4 weeks	
Reporting group title	8mg nitisinone
Reporting group description:	
8mg of nitisinone daily over 4 weeks	

Reporting group values	Untreated	1 mg	2mg nitisinone
Number of subjects	8	8	8
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	45.9	44.4	43.9
standard deviation	± 11.5	± 10.9	± 13.7
Gender categorical Units: Subjects			
Female	4	1	3
Male	4	7	5

Reporting group values	4mg nitisinone	8mg nitisinone	Total
Number of subjects	8	8	40
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	47.3	54.4	
standard deviation	± 10.7	± 7.3	-
Gender categorical			
Units: Subjects			
Female	3	2	13
Male	5	6	27

End points

End points reporting groups

Reporting group title	Untreated
Reporting group description:	
No treatment provided	
Reporting group title	1 mg
Reporting group description:	
1mg of nitisinone over 4 weeks	
Reporting group title	2mg nitisinone
Reporting group description:	
2mg nitisinone daily over 4 weeks	
Reporting group title	4mg nitisinone
Reporting group description:	
4mg of nitisinone daily over 4 weeks	
Reporting group title	8mg nitisinone
Reporting group description:	
8mg of nitisinone daily over 4 weeks	

Primary: u-HGA24 in patients with AKU after 4 weeks of nitisinone treatment

End point title	u-HGA24 in patients with AKU after 4 weeks of nitisinone treatment
End point description:	
24-hour urinary homogentisic acid excretion (u-HGA24) in patients with alkaptonuria after 4 weeks of treatment with nitisinone daily	
End point type	Primary
End point timeframe:	
Baseline to 4 weeks	

End point values	Untreated	1 mg	2mg nitisinone	4mg nitisinone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: mmol				
median (standard deviation)	31.0 (± 4.6)	3.9 (± 1.7)	1.6 (± 0.8)	0.7 (± 0.4)

End point values	8mg nitisinone			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mmol				
median (standard deviation)	0.1 (± 0.05)			

Statistical analyses

Statistical analysis title	u-HGA24 at Week 4

Statistical analysis description:

The primary variable, u-HGA24 at Week 4, was analysed using a mixed model for repeated measures (MMRM). The model included the study site, treatment group, visit, and the interaction between treatment group and visit as fixed factors and the baseline u-HGA24 as a covariate.

Comparison groups	Untreated v 1 mg v 2mg nitisinone v 4mg nitisinone v 8mg nitisinone
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.523
Method	Mixed models analysis

Secondary: Serum HGA after 4 weeks of treatment with nitisinone

End point title	Serum HGA after 4 weeks of treatment with nitisinone

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 4

End point values	Untreated	1 mg	2mg nitisinone	4mg nitisinone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	0[1]	0[2]	0[3]
Units: mmol				
median (standard deviation)	30.5 (± 12.4)	()	()	()

Notes:

[1] - Results not determined for this group.

[2] - Results not determined for this group.

[3] - Results not determined for this group.

End point values	8mg nitisinone			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: mmol				
median (standard deviation)	()			

Notes:
[4] - Results not determined for this group.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum tyrosine after 4 weeks of treatment with nitisinone

End point title	Serum tyrosine after 4 weeks of treatment with nitisinone

End point description:

End point type	Secondary

End point timeframe:
Baseline to week 4

End point values	Untreated	1 mg	2mg nitisinone	4mg nitisinone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: mmol/L				
median (standard deviation)	56 (± 15)	653 (± 106)	715 (± 171)	803 (± 155)

End point values	8mg nitisinone			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mmol/L				
median (standard deviation)	813 (± 145)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: The period for recording adverse events, begins from the time the subject has signed the informed consent until 28 days past the last dose of IMP	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	All participants

Reporting group description: -

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 32 (34.38%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
General disorders and administration site conditions			
Dizziness			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Eye disorders Eye pain subjects affected / exposed occurrences (all) Foreign body sensation in eyes subjects affected / exposed occurrences (all) Vitreous floaters subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1 1 / 32 (3.13%) 1 1 / 32 (3.13%) 1		
Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1 1 / 32 (3.13%) 1		
Respiratory, thoracic and mediastinal disorders Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Pain of skin subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1 1 / 32 (3.13%) 1 1 / 32 (3.13%) 1		
Musculoskeletal and connective tissue disorders			

Back injury subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle injury subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1 2 / 32 (6.25%) 2 1 / 32 (3.13%) 1		
Infections and infestations Oral herpes subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2013	Following advice from the MHRA the following changes were made to the Protocol; Addition of slit-lamp eye assessment Addition of Demographics, Inclusion/exclusion criteria and slit lamp eye assessment and removal of standardized meals from Schedule of Events Change of visit 2 from home visit to hospital attendance Addition of information regarding rescue procedure Clarification of clinically significant abnormalities being reporting as adverse events in the Laboratory safety assessment section Changes to PIS/ICF; Change of visit 2 from home visit to hospital attendance Addition of eye examination to overview of study procedures

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25475116