Clinical trial results:
Novel Assays for the Determination of Urinary 2,8-Dihydroxyadenine and Other Key Urinary Purine Metabolites - Rare Diseases Clinical Research Network Protocol Version 1

Summary

EudraCT number	2013-000975-33
Trial protocol	IS
Global end of trial date	02 January 2017

Results information

Result version number	v1 (current)
This version publication date	04 December 2021
First version publication date	04 December 2021

Trial information

Trial identification

Sponsor protocol code	RDCRN_RKSC_6412

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02752633
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Landspitali–The National University Hospital of Iceland
Sponsor organisation address	Hringbraut, Reykjavik, Iceland, 101
Public contact	Vidar Orn Edvardsson, Landspitali–The National University Hospital of Iceland, 354 8245227, vidare@lsh.is
Scientific contact	Vidar Orn Edvardsson, Landspitali–The National University Hospital of Iceland, 354 8245227, vidare@lsh.is

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	02 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 January 2017
Global end of trial reached?	Yes
Global end of trial date	02 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of 80 mg/day of febuxostat to 400 mg/day of allopurinol on the urinary excretion of 2,8-dihydroxyadenine in patients with APRT deficiency.

Protection of trial subjects:

This clinical trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements. This study will met the NIH definition of "greater than minimal risk" as the research procedures included a) the interruption of drug treatment for 2 weeks; b) substitution of allopurinol with febuxostat for 2 weeks in patients who had not taken febuxostat before the trial started; 3) the introduction of a new study drug, febuxostat (in a standard dose) introduced the minimal risk of adverse effects, different from that of allopurinol, which all participants were taking at study entry for the treatment of APRT deficiency; and 4) possibly an increase in the allopurinol dose, if the cases were taking less than 400 mg/day at study entry. Other than the above, this research did not pose additional risk to the patient beyond the risks for standard diagnosis and treatment of kidney stones and kidney disease. There were no real risks associated with a 24-hour urine collection, random urine collection; and the risks associated with venipuncture are minor. Interruption of drug therapy for two weeks posed minimal risks to participants. There was no physical risk to answering the study questions. There was the potential risk, though extremely unlikely, of loss of privacy. The data collected were anonymous and did not include personal identifiers. The investigators believe that there was no breach in privacy during the study.

Background therapy:

No such therapy was used.

Evidence for comparator:

The xanthine oxidoreductase (XOR) enzyme inhibitor allopurinol is an effective therapy for preventing new kidney stone formation, renal 2,8-dihydroxyadenine (DHA) deposition and progressive crystal nephropathy in individuals with adenine phosphoribosyltransferase deficiency (APRTd). The drug decreases DHA synthesis and urinary DHA excretion/crystalluria.(1, 2) Febuxostat, a selective non-purine XOR inhibitor,(2) has also been reported to decrease urinary DHA excretion/crystalluria in APRTd patients, providing an alternative treatment option for those who are intolerant of allopurinol. Based on our own personal experience some patients with minimal or no crystalluria continue to form stones while others with persistent crystalluria do not develop new stones or evidence of CKD progression. Thus, the dosing of XOR inhibitor (allopurinol and febuxostat) therapy has simply been empiric and has been modified by the degree of DHA crystalluria or by clinical events such as recurrent kidneys stones or progressive CKD. In adults, allopurinol has commonly been prescribed in doses ranging from 200 to 400 mg/day. Recently, our group developed a novel high-throughput ultra-performance liquid chromatography - electrospray tandem mass spectrometry (UPLC-MS/MS) assay for measurement of DHA in urine samples, which has the potential to greatly improve monitoring of pharmacotherapy in patients with APRTd.

1. Edvardsson V, Palsson R, Olafsson I, Hjaltadottir G, Laxdal T. Clinical features and genotype of adenine phosphoribosyltransferase deficiency in iceland. Am J Kidney Dis. 2001;38(3):473-80.
2. Runolfsdottir HL, Palsson R, Agustsdottir IM, Indridason OS, Edvardsson VO. Kidney Disease in Adenine Phosphoribosyltransferase Deficiency. Am J Kidney Dis. 2016;67(3):431-8.

Actual start date of recruitment	01 October 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	Iceland: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	8
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study participants were recruited from a group of patients with confirmed adenine phosphoribosyltransferase (APRT) deficiency, who were enrolled in the National Institutes of Health-supported APRT Deficiency Registry of the Rare Kidney Stone Consortium (RKSC, http://www.rarekidneystones.org/).

Pre-assignment

Screening details:

Confirmation of adenine phosphoribosyltransferase (APRT) deficiency was based upon the determination of known biallelic pathogenic APRT mutations or absent APRT enzyme activity in red blood cell lysates.

Pre-assignment period milestones

Number of subjects started	9
Number of subjects completed	9

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Washout 1

Arm description:

At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Allopurinol treatment

Arm description:

At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.

Arm type	Active comparator
Investigational medicinal product name	Allopurinol
Investigational medicinal product code	PR2
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.

Arm title	Febuxostat treatment

Arm description:

At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days.

Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.

Arm type	Active comparator
Investigational medicinal product name	Febuxostat
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.

Number of subjects in period 1	Washout 1	Allopurinol treatment	Febuxostat treatment
Started	9	8	8
Washout period 1	8	8	8
Allopurinol treatment	8	8	8
Febuxostat treatment	8	8	8
Completed	8	8	8
Not completed	1	0	0
Pregnancy	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Washout 1
Reporting group description:	
At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.	
Reporting group title	Allopurinol treatment
Reporting group description:	
At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.	
Reporting group title	Febuxostat treatment
Reporting group description:	
At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.	

Reporting group values	Washout 1	Allopurinol treatment	Febuxostat treatment
Number of subjects	9	8	8
Age categorical			
Study participants were recruited from a group of patients with confirmed APRT deficiency, who were enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium (RKSC, http://www.rarekidneystones.org/). Confirmation of APRT deficiency was based upon the determination of known biallelic pathogenic APRT mutations or absent APRT activity in red blood cell lysates.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	7	7
From 65-84 years	1	1	1
85 years and over	0	0	0
Age continuous			
Study participants were recruited from a group of patients with confirmed APRT deficiency, who were enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium (RKSC, http://www.rarekidneystones.org/). Confirmation of APRT deficiency was based upon the determination of known biallelic pathogenic APRT mutations or absent APRT activity in red blood cell lysates.			
Units: years			
median	54	54	54
full range (min-max)	28 to 67	28 to 67	28 to 67
Gender categorical			
Study participants were recruited from a group of patients with confirmed APRT deficiency, who were enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium (RKSC, http://www.rarekidneystones.org/). Confirmation of APRT deficiency was based upon the determination of known biallelic pathogenic APRT mutations or absent APRT activity			

in red blood cell lysates.			
Units: Subjects			
Female	5	4	4
Male	4	4	4

Reporting group values	Total		
Number of subjects	25		
Age categorical			
Study participants were recruited from a group of patients with confirmed APRT deficiency, who were enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium (RKSC, http://www.rarekidneystones.org/). Confirmation of APRT deficiency was based upon the determination of known biallelic pathogenic APRT mutations or absent APRT activity in red blood cell lysates.			
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)	22		
From 65-84 years	3		
85 years and over	0		
Age continuous			
Study participants were recruited from a group of patients with confirmed APRT deficiency, who were enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium (RKSC, http://www.rarekidneystones.org/). Confirmation of APRT deficiency was based upon the determination of known biallelic pathogenic APRT mutations or absent APRT activity in red blood cell lysates.			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Study participants were recruited from a group of patients with confirmed APRT deficiency, who were enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium (RKSC, http://www.rarekidneystones.org/). Confirmation of APRT deficiency was based upon the determination of known biallelic pathogenic APRT mutations or absent APRT activity in red blood cell lysates.			
Units: Subjects			
Female	13		
Male	12		

End points

End points reporting groups

Reporting group title	Washout 1
Reporting group description:	
At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.	
Reporting group title	Allopurinol treatment
Reporting group description:	
At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.	
Reporting group title	Febuxostat treatment
Reporting group description:	
At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.	

Primary: Urinary 2,8-dihydroxyadenine excretion

End point title	Urinary 2,8-dihydroxyadenine excretion
End point description:	
This is a clinical trial comparing the effect of 80 mg/day of febuxostat to 400 mg/day of allopurinol on the urinary excretion of 2,8-dihydroxyadenine in patients with APRT deficiency.	
End point type	Primary
End point timeframe:	
Urinary 2,8-dihydroxyadenine excretion was evaluated at days 7, 21, and 42	

End point values	Washout 1	Allopurinol treatment	Febuxostat treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: mg				
number (not applicable)	9	8	8	

Attachments (see zip file)	Results_text/Results_text.pdf Table 1/Table 1.pdf Table 2.pdf Table 3/Table 3.pdf Table 4/Table 4.pdf

Statistical analyses

Statistical analysis title	Endpoint analysis

Statistical analysis description:

Differences in the median urinary DHA excretion and the urinary DHA/Cr ratio between periods off pharmacotherapy and on treatment with the two study drugs, allopurinol and febuxostat, were assessed using the Wilcoxon signed-rank test.

Comparison groups	Allopurinol treatment v Febuxostat treatment v Washout 1
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Notes:

[1] - Data are presented as a median (range). Differences in the median urinary DHA excretion and the urinary DHA-to-creatinine ratio between periods off pharmacotherapy (washout period 1) and on the two study drugs, febuxostat and allopurinol, were assessed using the Wilcoxon signed rank test.

Primary: Urinary DHA-to-creatinine ratio

End point title	Urinary DHA-to-creatinine ratio

End point description:

This is a clinical trial comparing the effect of 80 mg/day of febuxostat to 400 mg/day of allopurinol on the urinary excretion of 2,8-dihydroxyadenine in patients with APRT deficiency.

End point type	Primary

End point timeframe:

The urinary DHA-to-creatinine ratio was evaluated at days 0, 21 and 42

End point values	Washout 1	Allopurinol treatment	Febuxostat treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: mg DHA/microg creatinine				
number (not applicable)	9	8	8	

Statistical analyses

Statistical analysis title	Endpoint analysis
Comparison groups	Allopurinol treatment v Febuxostat treatment v Washout 1
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Continuous during the study period.

Adverse event reporting additional description:

Continuous during the study period.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Washout 1

Reporting group description:

At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.

Reporting group title	Allopurinol treatment

Reporting group description:

At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.

Reporting group title	Febuxostat treatment

Reporting group description:

At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days.

Serious adverse events	Washout 1	Allopurinol treatment	Febuxostat treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Washout 1	Allopurinol treatment	Febuxostat treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: The study only had 8 participants. Doses were moderate. Treatment period was short. No adverse events reported by participants.

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.

Limitations inherent in this study include a small number of participants as expected for a rare disease.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29241594