Clinical trial results:
A randomised, doublet blinded, placebo controlled cross-over study of Allopurinols effect to prevent loss of kidney function in type 1 diabetes

Summary

EudraCT number	2014-001786-26
Trial protocol	DK
Global end of trial date	12 August 2016

Results information

Result version number	v1 (current)
This version publication date	31 January 2018
First version publication date	31 January 2018
Summary attachment (see zip file)	Summary of MIKAL study (EudraCT summary MIKAL.pdf)

Trial information

Trial identification

Sponsor protocol code	3004

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Steno Diabetes Center
Sponsor organisation address	Niels Steensensvej 2-6, Gentofte, Denmark, 2820
Public contact	Diabetes complications research , Steno Diabetes Center, +45 30912975, sascha.maria.pilemann-lyberg@regionh.dk
Scientific contact	Diabetes complications research , Steno Diabetes Center, +45 30912975, sascha.maria.pilemann-lyberg@regionh.dk

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	07 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether lowering serum uric acid by means of allopurinol early in the course of kidney disease may be effective in slowing the decline of renal function in T1D patients.

Protection of trial subjects:

Blood samples for HbA1c, white blood count, electrolytes, hemoglobin and skin assessment was used to monitor any side effects or distress of the subjects.

Background therapy:

Insulin treatment and RAAS blockers

Evidence for comparator: -

Actual start date of recruitment	01 September 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	Denmark: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	21
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

30 Subjects with type 1 diabetes (WHO criteria), uric acid ≥ 0.26 mmol/l, persistent albuminuria (UACR: urine albumin creatinine ratio ≥30 mg/g in at least 2 out of 3 consecutive morning spot urine samples) and CKD-EPI-eGFR ≥ 40 ml/min/1.73m2. Recruitment started September 2014 and ended January 2016.

Pre-assignment

Screening details:

64 subjects were screened and 34 failed screening due to low uric acid level, low eGFR or not albuminuric.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo treatment period

Arm description:

Subjects were treated with placebo for 60 days either as there first treatment or after a 4 week wash out period after the first treatment.

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

Dosage and administration details:

400 mg per day

Arm title	Active treatment with allopurinol

Arm description:

Subjects either started active treatment as there first treatment or after a 4 week wash out period.

Arm type	Active comparator
Investigational medicinal product name	Allopurinol "DAK"
Investigational medicinal product code	M04AA01
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg per day

Number of subjects in period 1	Placebo treatment period	Active treatment with allopurinol
Started	15	15
Cr51-EDTA-GFR	15	12
Completed	15	12
Not completed	0	3
Adverse event, non-fatal	-	3

Period 2	
Period 2 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Active treatment with allopurinol

Arm description:

Subjects enter active treatment after 4 weeks of wash out

Arm type	Active comparator
Investigational medicinal product name	Allopurinol "DAK"
Investigational medicinal product code	M04AA01
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg pr day

Arm title	Placebo treatment period

Arm description:

Subjects started placebo treatment after a 4 week period wash out

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

Dosage and administration details:

400 mg pr. day

Number of subjects in period 2	Active treatment with allopurinol	Placebo treatment period
Started	15	12
Cr51-EDTA-GFR	14	12
Completed	14	12
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

End points

End points reporting groups

Reporting group title	Placebo treatment period
Reporting group description:	
Subjects were treated with placebo for 60 days either as there first treatment or after a 4 week wash out period after the first treatment.	
Reporting group title	Active treatment with allopurinol
Reporting group description:	
Subjects either started active treatment as there first treatment or after a 4 week wash out period.	
Reporting group title	Active treatment with allopurinol
Reporting group description:	
Subjects enter active treatment after 4 weeks of wash out	
Reporting group title	Placebo treatment period
Reporting group description:	
Subjects started placebo treatment after a 4 week period wash out	
Subject analysis set title	paired t test
Subject analysis set type	Full analysis
Subject analysis set description:	
First the data was subjected to analysis to confirm that there is no carry-over effect and when this was confirmed the to treatment arms "allopurinol" and "placebo" was compared with a paired ttest.	

Primary: change in albuminuria

End point title	change in albuminuria
End point description:	
End point type	Primary
End point timeframe:	
Albuminuria was measured at the last day of treatment (after 60 days of treatment with either Allopurinol or placebo).	

End point values	Placebo treatment period	Active treatment with allopurinol	Active treatment with allopurinol	Placebo treatment period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	11	14	10
Units: mg/24h				
median (standard deviation)	403 (± 611)	523 (± 495)	403 (± 853)	351 (± 240)

End point values	paired t test			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: mg/24h				
median (standard deviation)	456 (± 707)			

Statistical analyses

Statistical analysis title	Paired ttest
Statistical analysis description:	
Paired ttest was used to compare treatment periods allopurinol vs. placebo	
Comparison groups	Placebo treatment period v Active treatment with allopurinol
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: changes in Cr51-EDTA-GFR

End point title	changes in Cr51-EDTA-GFR
End point description:	
End point type	Secondary
End point timeframe:	
Cr51-EDTA-GFR was measured at the last treatment day (after 60 days of treatment with either Allopurinol or placebo)	

End point values	Placebo treatment period	Active treatment with allopurinol	Active treatment with allopurinol	Placebo treatment period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	12	14	12
Units: ml/min/1.73m2				
median (standard deviation)	69 (± 20)	79 (± 21)	70 (± 19)	75 (± 22)

End point values	paired t test			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: ml/min/1.73m2				

median (standard deviation)	74 (± 20)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

4 subjects experienced adverse event. All adverse events occurred after initiation study medication and was assed by a doctor immediately after the subject reported the adverse event.

Adverse event reporting additional description:

2 had gastrointestinal discomfort, 2 had universal skin rash

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	3

Reporting groups

Reporting group title	Skin Rash

Reporting group description:

Universal skin rash after initiating study medication

Reporting group title	Gastroentestinal discomfort

Reporting group description: -

Reporting group title	irregular heart rythm

Reporting group description: -

Serious adverse events	Skin Rash	Gastroentestinal discomfort	irregular heart rythm
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
irregular heart rhythm	Additional description: one had irregular heart rhythm but was known with this previously and was without study medication when it occurred.		
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Skin Rash	Gastroentestinal discomfort	irregular heart rythm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	0 / 30 (0.00%)
Gastrointestinal disorders			

gastroentestinal discomfort	Additional description: Two experienced gastrointestinal discomfort.		
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	2	2	0
Skin and subcutaneous tissue disorders			
Universal rash	Additional description: two subjects experienced universal skin rash after intiating study medicantion. Was gone after stopping with study medication.		
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	2	2	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.

The treatment period was to short to show an effect on the end point.

Notes: