Clinical trial results:
Does oral sodium bicarbonate therapy improve function and quality of life in older patients with chronic kidney disease and low-grade acidosis? A multicentre randomized placebo controlled trial

Summary

EudraCT number	2011-005271-16
Trial protocol	GB
Global end of trial date	28 February 2018

Results information

Result version number	v1 (current)
This version publication date	09 March 2019
First version publication date	09 March 2019

Trial information

Trial identification

Sponsor protocol code	2010NE02

Additional study identifiers

ISRCTN number	ISRCTN09486651
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	MREC: 12/ES/0023

Notes:

Sponsors

Sponsor organisation name	Tayside Academic Health Science Centre
Sponsor organisation address	Ninewells Hospital, Dundee, United Kingdom, DD1 9SY
Public contact	Margaret Band, Tayside Clinical Trials Unit, +44 01382383993, m.band@dundee.ac.uk
Scientific contact	Margaret Band, Tayside Clinical Trials Unit, +44 01382383993, m.band@dundee.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 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2018
Global end of trial reached?	Yes
Global end of trial date	28 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether oral bicarbonate therapy improves physical function and health-related quality of life compared to placebo in older people with Chronic Kidney Disease (CKD) and mild acidosis

Protection of trial subjects:

Nil specific to this intervention. Regular clinical review and telephone contact to detect adverse events.

Background therapy:

Usual care

Evidence for comparator:

Placebo used as comparator

Actual start date of recruitment	01 November 2012
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: 300
Worldwide total number of subjects	300
EEA total number of subjects	300

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)	26
From 65 to 84 years	256
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

Participants recruited from 27 UK centres between May 2013 and February 2017

Pre-assignment

Screening details:

410 screened. Reasons for ineligibility: serum bicarbonate >21mmol/L (n=81). eGFR >30ml/min/1.73m2 (n=37). Uncontrolled hypertension (n=9). Commenced on sodium bicarbonate at screening (n=4). other medical contraindication (n=6). Unable to comply with study requirements (n=1). Did not wish to continue after screening visit (n=3)

Period 1

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

Blinding implementation details:

Matching placebo used; identical bottles, allocated by web-based randomisation system. Dummy uptitration used to ensure masking during dose escalation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bicarbonate

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sodium Bicarbonate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500mg three times a day, titrated up to 1 gram three times a day after 3 months if serum bicarbonate <22mmol/L

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

1 tablet three times a day; uptitrated to 2 tablets 3 times a day after 3 months if serum bicarbonate <22mmol/L

Number of subjects in period 1	Bicarbonate	Placebo
Started	152	148
Completed	81	80
Not completed	71	68
Adverse event, serious fatal	15	11
Physician decision	2	4
Consent withdrawn by subject	33	35
Adverse event, non-fatal	5	5
Miscellaneous	1	4
Lost to follow-up	2	-
Truncated follow up	13	9

Baseline characteristics

Reporting groups	
Reporting group title	Bicarbonate
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Bicarbonate	Placebo	Total
Number of subjects	152	148	300
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			
arithmetic mean	73.9	74.0	
standard deviation	± 7.6	± 6.6	-
Gender categorical Units: Subjects			
Female	42	44	86
Male	110	104	214
Mean eGFR			
Estimated glomerular filtration rate derived via MDRD4 equation			
Units: ml/min/1.73m2			
arithmetic mean	19.7	18.2	
standard deviation	± 6.5	± 6.4	-
Serum bicarbonate Units: mmol/L			
arithmetic mean	20.6	20.1	
standard deviation	± 2.6	± 2.5	-
Short Physical Performance Battery Units: Units			
arithmetic mean	8.0	8.1	
standard deviation	± 2.4	± 2.2	-

End points

End points reporting groups

Reporting group title	Bicarbonate
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Short Physical Performance Battery at 12 months

End point title	Short Physical Performance Battery at 12 months
End point description:	
End point type	Primary
End point timeframe: 12 months	

End point values	Bicarbonate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	104		
Units: Units				
arithmetic mean (standard deviation)	8.3 (± 2.5)	8.8 (± 2.2)		

Statistical analyses

Statistical analysis title	Between-group difference
Comparison groups	Bicarbonate v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.15
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.1

Notes:

[1] - Adjusted for baseline SPPB, age, sex and CKD category

Secondary: EQ5D-3L

End point title	EQ5D-3L

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Bicarbonate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	80		
Units: units				
arithmetic mean (standard deviation)	0.72 (± 0.24)	0.75 (± 0.19)		

Statistical analyses

Statistical analysis title	EQ5D repeated measures between group comparison
Comparison groups	Bicarbonate v Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.06
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0

Notes:

[2] - Adjusted for baseline EQ5D, age,sex and CKD category

Secondary: Serum bicarbonate

End point title	Serum bicarbonate

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Bicarbonate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	80		
Units: mmol/L				
arithmetic mean (standard deviation)	22.9 (± 4.1)	22.5 (± 3.3)		

Statistical analyses

Statistical analysis title	Repeated measures between-groups analysis
Comparison groups	Bicarbonate v Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.6

Notes:

[3] - Adjusted for baseline bicarbonate, age, sex and CKD stage

Secondary: eGFR

End point title	eGFR

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Bicarbonate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	80		
Units: ml/min/1.73m2				
arithmetic mean (standard deviation)	19.5 (± 10.2)	18.0 (± 8.2)		

Statistical analyses

Statistical analysis title	Repeated measures between groups analysis
Comparison groups	Bicarbonate v Placebo

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.39
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	2

Notes:

[4] - Adjusted for baseline eGFR, age and sex

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening visit to last visit (24 months or point of dropout)

Adverse event reporting additional description:

Note that total number of AEs was 457 in the bicarbonate arm, and 400 in the placebo arm. Majority of AEs spread across multiple preferred terms and hence not reaching the 5% reporting threshold

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Bicarbonate

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Bicarbonate	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 152 (3.95%)	6 / 148 (4.05%)	
number of deaths (all causes)	15	11	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Adverse drug reaction			
subjects affected / exposed	0 / 152 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy toxic			
subjects affected / exposed	0 / 152 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Ill-defined disorder			
subjects affected / exposed	1 / 152 (0.66%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Colitis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 152 (0.66%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 152 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 152 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Volvulus			
subjects affected / exposed	1 / 152 (0.66%)	0 / 148 (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			
Drug eruption			
subjects affected / exposed	0 / 152 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal haematoma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis reactive			

subjects affected / exposed	1 / 152 (0.66%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 148 (0.68%)	
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: 5 %

Non-serious adverse events	Bicarbonate	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 152 (30.26%)	46 / 148 (31.08%)	
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection			
subjects affected / exposed	23 / 152 (15.13%)	24 / 148 (16.22%)	
occurrences (all)	23	24	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	23 / 152 (15.13%)	24 / 148 (16.22%)	
occurrences (all)	23	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 January 2015	Series of amendments to relax the inclusion/exclusion criteria. Protocol as published reflects the final amended protocol used for the trial. See: Witham MD et al. Trials. 2015 Aug 1;16:326. doi: 10.1186/s13063-015-0843-6.

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/26231610