



## Clinical trial results:

### A Feasibility Randomised Controlled Trial: Effects of Oral Sodium Bicarbonate Supplementation in Patients on Haemodialysis

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-001439-20 |
| Trial protocol           | GB             |
| Global end of trial date | 03 May 2016    |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 03 January 2020 |
| First version publication date | 03 January 2020 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 15HH2613 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02692378 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |                                                                                                    |
|------------------------------|----------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Imperial College Healthcare NHS Trust                                                              |
| Sponsor organisation address | Du Cane Road, London, United Kingdom, W12 0HS                                                      |
| Public contact               | Dr Damien Ashby , Imperial College Healthcare NHS Trust ,<br>+44 02033135171, damien.ashby@nhs.net |
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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:

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**Results analysis stage**

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|                                                      |             |
|------------------------------------------------------|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 03 May 2017 |
| Is this the analysis of the primary completion data? | Yes         |
| Primary completion date                              | 03 May 2016 |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 03 May 2016 |
| Was the trial ended prematurely?                     | No          |

Notes:

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**General information about the trial**

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Main objective of the trial:

Principal research question:

What are the effects of oral sodium bicarbonate supplementation in haemodialysis patients?

Principal objective:

Investigate the effect of oral sodium bicarbonate supplementation on blood potassium levels throughout the dialysis cycle (pre and post dialysis potassium and intradialysis potassium gradient).

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Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 01 June 2015 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 43 |
| Worldwide total number of subjects   | 43                 |
| EEA total number of subjects         | 43                 |

Notes:

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**Subjects enrolled per age group**

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|                                           |    |
|-------------------------------------------|----|
| 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)                      | 28 |
| From 65 to 84 years                       | 15 |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from three satellite haemodialysis units at Imperial NHS Trust between June 2015 and May 2016.

### Pre-assignment

Screening details:

518 patients were screened and 130 were eligible for enrolment, finally enrolled 43 patients.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Run-in phase            |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Control |

Arm description:

Standard haemodialysis treatment thrice weekly using a standard dialysate containing bicarbonate at a concentration of 35mmols/L (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l).

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Arm type                                                  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Sodium Bicarbonate |
|------------------|--------------------|

Arm description:

Standard haemodialysis treatment thrice weekly, using a standard dialysate containing bicarbonate at a concentration of 35mmols/ (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l), no treatment in run-in phase.

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | no intervention   |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Capsule, hard     |
| Routes of administration               | Other use         |

Dosage and administration details:

No intervention

| Number of subjects in period 1 | Control | Sodium Bicarbonate |
|--------------------------------|---------|--------------------|
| Started                        | 22      | 21                 |
| Completed                      | 19      | 16                 |
| Not completed                  | 3       | 5                  |
| Consent withdrawn by subject   | 3       | 5                  |

**Period 2**

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Treatment phase         |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

**Arms**

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Control |

Arm description:

Standard haemodialysis treatment thrice weekly using a standard dialysate containing bicarbonate at a concentration of 35mmols/L (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l).

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Arm type                                                  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Sodium Bicarbonate |
|------------------|--------------------|

Arm description:

Standard haemodialysis treatment thrice weekly, using a standard dialysate containing bicarbonate at a concentration of 35mmols/ (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l) with the addition of oral sodium bicarbonate 500mg capsules for 12 weeks (weeks 5-16 of the study).

The dosage titrated to individual blood levels. Starting dose was 1g twice daily with the dose titrated during the first 4 weeks of treatment (increasing by 0.5g twice daily as tolerated, to a maximum of 3g bd) to achieve predialysis bicarbonate levels over 22mmols/L.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Sodium bicarbonate |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Capsule, hard      |
| Routes of administration               | Oral use           |

Dosage and administration details:

Starting dose 1g bd (4 tablets per day) with the dose titrated during the first 4 weeks of treatment (increasing by 0.5g bd as tolerated, to a maximum 3g bd) to achieve predialysis bicarbonate over 22mmol/l.

| <b>Number of subjects in period 2</b> | Control | Sodium Bicarbonate |
|---------------------------------------|---------|--------------------|
| Started                               | 19      | 16                 |
| Completed                             | 18      | 15                 |
| Not completed                         | 1       | 1                  |
| Renal transplant                      | 1       | 1                  |

**Period 3**

|                              |                         |
|------------------------------|-------------------------|
| Period 3 title               | Wash out phase          |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

**Arms**

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Control |
|------------------|---------|

Arm description:

Standard haemodialysis treatment thrice weekly using a standard dialysate containing bicarbonate at a concentration of 35mmols/L (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l).

|          |                 |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Sodium Bicarbonate |
|------------------|--------------------|

Arm description:

Standard haemodialysis treatment thrice weekly, using a standard dialysate containing bicarbonate at a concentration of 35mmols/ (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l), no treatment just follow-up

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | no intervention |
|----------------------------------------|-----------------|

|                                        |  |
|----------------------------------------|--|
| Investigational medicinal product code |  |
|----------------------------------------|--|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |               |
|----------------------|---------------|
| Pharmaceutical forms | Capsule, hard |
|----------------------|---------------|

|                          |           |
|--------------------------|-----------|
| Routes of administration | Other use |
|--------------------------|-----------|

Dosage and administration details:

no intervention

| Number of subjects in period 3 | Control | Sodium Bicarbonate |
|--------------------------------|---------|--------------------|
| Started                        | 18      | 15                 |
| Completed                      | 18      | 15                 |

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description:

Standard haemodialysis treatment thrice weekly using a standard dialysate containing bicarbonate at a concentration of 35mmols/L (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Sodium Bicarbonate |
|-----------------------|--------------------|

Reporting group description:

Standard haemodialysis treatment thrice weekly, using a standard dialysate containing bicarbonate at a concentration of 35mmols/ (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l), no treatment in run-in phase.

| Reporting group values                           | Control | Sodium Bicarbonate | Total |
|--------------------------------------------------|---------|--------------------|-------|
| Number of subjects                               | 22      | 21                 | 43    |
| Age categorical                                  |         |                    |       |
| Units: Subjects                                  |         |                    |       |
| Adults (18-64 years)                             | 14      | 13                 | 27    |
| From 65-84 years                                 | 8       | 8                  | 16    |
| Age continuous                                   |         |                    |       |
| Units: years                                     |         |                    |       |
| median                                           | 61      | 61                 |       |
| standard deviation                               | ± 9.7   | ± 14               | -     |
| Gender categorical                               |         |                    |       |
| Units: Subjects                                  |         |                    |       |
| Female                                           | 5       | 5                  | 10    |
| Male                                             | 17      | 16                 | 33    |
| Haemodialysis vintage                            |         |                    |       |
| The time participants have been on haemodialysis |         |                    |       |
| Units: months                                    |         |                    |       |
| median                                           | 38      | 32                 |       |
| standard deviation                               | ± 46    | ± 48               | -     |

### Subject analysis sets

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | Non-bic Control |
|----------------------------|-----------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Measurements over the first 4 weeks (run-in phase) and last 4 weeks (wash out phase) to establish blood potassium profile.

|                            |                            |
|----------------------------|----------------------------|
| Subject analysis set title | Non-bic Sodium Bicarbonate |
|----------------------------|----------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Measurements over the first 4 weeks (run-in phase) and last 4 weeks (wash out phase) to establish blood potassium profile.

| Reporting group values | Non-bic Control | Non-bic Sodium Bicarbonate |  |
|------------------------|-----------------|----------------------------|--|
| Number of subjects     | 19              | 15                         |  |

|                                                  |           |          |  |
|--------------------------------------------------|-----------|----------|--|
| Age categorical                                  |           |          |  |
| Units: Subjects                                  |           |          |  |
| Adults (18-64 years)                             | 14        | 13       |  |
| From 65-84 years                                 | 4         | 2        |  |
| Age continuous                                   |           |          |  |
| Units: years                                     |           |          |  |
| median                                           | 61        | 61       |  |
| standard deviation                               | $\pm 9.7$ | $\pm 14$ |  |
| Gender categorical                               |           |          |  |
| Units: Subjects                                  |           |          |  |
| Female                                           | 4         | 3        |  |
| Male                                             | 15        | 12       |  |
| Haemodialysis vintage                            |           |          |  |
| The time participants have been on haemodialysis |           |          |  |
| Units: months                                    |           |          |  |
| median                                           | 38        | 32       |  |
| standard deviation                               | $\pm 46$  | $\pm 48$ |  |

## End points

### End points reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description:

Standard haemodialysis treatment thrice weekly using a standard dialysate containing bicarbonate at a concentration of 35mmols/L (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Sodium Bicarbonate |
|-----------------------|--------------------|

Reporting group description:

Standard haemodialysis treatment thrice weekly, using a standard dialysate containing bicarbonate at a concentration of 35mmols/ (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l), no treatment in run-in phase.

|                       |         |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description:

Standard haemodialysis treatment thrice weekly using a standard dialysate containing bicarbonate at a concentration of 35mmols/L (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Sodium Bicarbonate |
|-----------------------|--------------------|

Reporting group description:

Standard haemodialysis treatment thrice weekly, using a standard dialysate containing bicarbonate at a concentration of 35mmols/ (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l) with the addition of oral sodium bicarbonate 500mg capsules for 12 weeks (weeks 5-16 of the study).

The dosage titrated to individual blood levels. Starting dose was 1g twice daily with the dose titrated during the first 4 weeks of treatment (increasing by 0.5g twice daily as tolerated, to a maximum of 3g bd) to achieve predialysis bicarbonate levels over 22mmols/L.

|                       |         |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description:

Standard haemodialysis treatment thrice weekly using a standard dialysate containing bicarbonate at a concentration of 35mmols/L (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Sodium Bicarbonate |
|-----------------------|--------------------|

Reporting group description:

Standard haemodialysis treatment thrice weekly, using a standard dialysate containing bicarbonate at a concentration of 35mmols/ (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l), no treatment just follow-up

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | Non-bic Control |
|----------------------------|-----------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Measurements over the first 4 weeks (run-in phase) and last 4 weeks (wash out phase) to establish blood potassium profile.

|                            |                            |
|----------------------------|----------------------------|
| Subject analysis set title | Non-bic Sodium Bicarbonate |
|----------------------------|----------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Measurements over the first 4 weeks (run-in phase) and last 4 weeks (wash out phase) to establish blood potassium profile.

### Primary: Inter-dialytic Change in Dialysis Potassium Level (Pre and Post Dialysis Potassium Level)

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Inter-dialytic Change in Dialysis Potassium Level (Pre and Post Dialysis Potassium Level) |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

20 weeks

| <b>End point values</b>             | Control            | Sodium Bicarbonate | Non-bic Control      | Non-bic Sodium Bicarbonate |
|-------------------------------------|--------------------|--------------------|----------------------|----------------------------|
| Subject group type                  | Reporting group    | Reporting group    | Subject analysis set | Subject analysis set       |
| Number of subjects analysed         | 19                 | 15                 | 19                   | 15                         |
| Units: mmol/L                       |                    |                    |                      |                            |
| geometric mean (standard deviation) | 2.00 ( $\pm$ 0.63) | 1.69 ( $\pm$ 0.49) | 2.08 ( $\pm$ 0.64)   | 1.9 ( $\pm$ 0.60)          |

### Statistical analyses

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| <b>Statistical analysis title</b>       | Change in Dialysis Potassium - Sodium Bicarbonate |
| Comparison groups                       | Sodium Bicarbonate v Non-bic Sodium Bicarbonate   |
| Number of subjects included in analysis | 30                                                |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | superiority                                       |
| P-value                                 | = 0.032                                           |
| Method                                  | paired t-test                                     |

|                                         |                                        |
|-----------------------------------------|----------------------------------------|
| <b>Statistical analysis title</b>       | Change in Dialysis Potassium - Control |
| Comparison groups                       | Control v Non-bic Control              |
| Number of subjects included in analysis | 38                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.33                                 |
| Method                                  | paired t-test                          |

### Secondary: Changes in QT dispersion, 12 lead Electrocardiogram analysis

|                        |                                                              |
|------------------------|--------------------------------------------------------------|
| End point title        | Changes in QT dispersion, 12 lead Electrocardiogram analysis |
| End point description: |                                                              |
| End point type         | Secondary                                                    |
| End point timeframe:   |                                                              |
| 20 weeks               |                                                              |

| End point values                    | Control           | Sodium Bicarbonate | Non-bic Control      | Non-bic Sodium Bicarbonate |
|-------------------------------------|-------------------|--------------------|----------------------|----------------------------|
| Subject group type                  | Reporting group   | Reporting group    | Subject analysis set | Subject analysis set       |
| Number of subjects analysed         | 19                | 15                 | 19                   | 15                         |
| Units: ms                           |                   |                    |                      |                            |
| geometric mean (standard deviation) | 8.8 ( $\pm$ 21.4) | 10.4 ( $\pm$ 27.5) | 8.7 ( $\pm$ 39.9)    | 8.8 ( $\pm$ 23)            |

## Statistical analyses

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| <b>Statistical analysis title</b>       | Change in QT dispersion_control |
| Statistical analysis description:       |                                 |
| Control group                           |                                 |
| Comparison groups                       | Control v Non-bic Control       |
| Number of subjects included in analysis | 38                              |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | = 0.98                          |
| Method                                  | paired t-test                   |

|                                         |                                                 |
|-----------------------------------------|-------------------------------------------------|
| <b>Statistical analysis title</b>       | Change in QT dispersion Sodium bicarbonate      |
| Comparison groups                       | Sodium Bicarbonate v Non-bic Sodium Bicarbonate |
| Number of subjects included in analysis | 30                                              |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | = 0.79                                          |
| Method                                  | paired t-test                                   |

## Secondary: Changes in Lean Tissue Mass

|                                                                                                                                   |                             |
|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                   | Changes in Lean Tissue Mass |
| End point description:                                                                                                            |                             |
| Body composition measurement before dialysis with the validated body composition monitor by Fresenius to measure lean tissue mass |                             |
| Analysis of lean tissue mass between the start and end of the treatment phase of the study                                        |                             |
| End point type                                                                                                                    | Secondary                   |
| End point timeframe:                                                                                                              |                             |
| 12 weeks                                                                                                                          |                             |

| End point values                     | Control            | Sodium Bicarbonate | Control            | Sodium Bicarbonate |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type                   | Reporting group    | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed          | 18                 | 15                 | 18                 | 15                 |
| Units: percentage of lean mass       |                    |                    |                    |                    |
| arithmetic mean (standard deviation) | 51.8 ( $\pm$ 13.7) | 45.0 ( $\pm$ 12.2) | 50.2 ( $\pm$ 12.1) | 45.5 ( $\pm$ 12.5) |

### Statistical analyses

|                                         |                                                |
|-----------------------------------------|------------------------------------------------|
| <b>Statistical analysis title</b>       | Changes in Lean Tissue Mass_Sodium Bicarbonate |
| Comparison groups                       | Sodium Bicarbonate v Sodium Bicarbonate        |
| Number of subjects included in analysis | 30                                             |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | = 0.58                                         |
| Method                                  | paired t-test                                  |

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>       | Changes in Lean Tissue Mass Control |
| Comparison groups                       | Control v Control                   |
| Number of subjects included in analysis | 36                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.041                             |
| Method                                  | paired t-test                       |

### Secondary: Handgrip Strength

|                        |                   |
|------------------------|-------------------|
| End point title        | Handgrip Strength |
| End point description: |                   |
| End point type         | Secondary         |
| End point timeframe:   |                   |
| 12 weeks               |                   |

| End point values                       | Control         | Sodium Bicarbonate | Control             | Sodium Bicarbonate  |
|----------------------------------------|-----------------|--------------------|---------------------|---------------------|
| Subject group type                     | Reporting group | Reporting group    | Reporting group     | Reporting group     |
| Number of subjects analysed            | 18              | 15                 | 18                  | 15                  |
| Units: kg                              |                 |                    |                     |                     |
| arithmetic mean (full range (min-max)) | 31.2 (14 to 51) | 26.6 (10 to 64)    | 29.7 (14.3 to 51.8) | 26.2 (15.9 to 64.5) |

### Statistical analyses

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>       | Handgrip Strength Sodium Bicarbonate    |
| Comparison groups                       | Sodium Bicarbonate v Sodium Bicarbonate |
| Number of subjects included in analysis | 30                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.64                                  |
| Method                                  | paired t-test                           |

|                                         |                           |
|-----------------------------------------|---------------------------|
| <b>Statistical analysis title</b>       | Handgrip Strength Control |
| Comparison groups                       | Control v Control         |
| Number of subjects included in analysis | 36                        |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.034                   |
| Method                                  | paired t-test             |

### Secondary: Changes in Total Symptom Severity

|                        |                                   |
|------------------------|-----------------------------------|
| End point title        | Changes in Total Symptom Severity |
| End point description: |                                   |
| End point type         | Secondary                         |
| End point timeframe:   |                                   |
| 20 weeks               |                                   |

| End point values                     | Control         | Sodium Bicarbonate | Non-bic Control      | Non-bic Sodium Bicarbonate |
|--------------------------------------|-----------------|--------------------|----------------------|----------------------------|
| Subject group type                   | Reporting group | Reporting group    | Subject analysis set | Subject analysis set       |
| Number of subjects analysed          | 19              | 15                 | 18                   | 15                         |
| Units: score on scale                |                 |                    |                      |                            |
| arithmetic mean (standard deviation) | 11.3 (± 7.4)    | 8.9 (± 6.6)        | 14.1 (± 9.6)         | 11.9 (± 9.2)               |

### Statistical analyses

|                                         |                                                 |
|-----------------------------------------|-------------------------------------------------|
| <b>Statistical analysis title</b>       | Total Symptom Severity Sodium Bicarbonate       |
| Comparison groups                       | Sodium Bicarbonate v Non-bic Sodium Bicarbonate |
| Number of subjects included in analysis | 30                                              |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | = 0.1                                           |
| Method                                  | paired t-test                                   |

|                                         |                                        |
|-----------------------------------------|----------------------------------------|
| <b>Statistical analysis title</b>       | Copy of Total Symptom Severity Control |
| Comparison groups                       | Control v Non-bic Control              |
| Number of subjects included in analysis | 37                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.12                                 |
| Method                                  | paired t-test                          |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

20 weeks

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description:

Standard haemodialysis treatment thrice weekly using a standard dialysate containing bicarbonate at a concentration of 35mmols/L (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Sodium Bicarbonate |
|-----------------------|--------------------|

Reporting group description:

Standard haemodialysis treatment thrice weekly, using a standard dialysate containing bicarbonate at a concentration of 35mmols/ (final dialysate bicarbonate 32mmol/l with acetate 3mmol/l), no treatment in run-in phase.

| Serious adverse events                            | Control         | Sodium Bicarbonate |  |
|---------------------------------------------------|-----------------|--------------------|--|
| Total subjects affected by serious adverse events |                 |                    |  |
| subjects affected / exposed                       | 5 / 22 (22.73%) | 1 / 21 (4.76%)     |  |
| number of deaths (all causes)                     | 0               | 0                  |  |
| number of deaths resulting from adverse events    | 0               | 0                  |  |
| Nervous system disorders                          |                 |                    |  |
| Cerebral infarct                                  |                 |                    |  |
| subjects affected / exposed                       | 0 / 22 (0.00%)  | 1 / 21 (4.76%)     |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1              |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0              |  |
| Brain bleed                                       |                 |                    |  |
| subjects affected / exposed                       | 1 / 22 (4.55%)  | 0 / 21 (0.00%)     |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0              |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0              |  |
| Gastrointestinal disorders                        |                 |                    |  |
| Rectus sheath haematoma                           |                 |                    |  |
| subjects affected / exposed                       | 1 / 22 (4.55%)  | 0 / 21 (0.00%)     |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0              |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0              |  |
| Hepatobiliary disorders                           |                 |                    |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Gallstone pancreatitis                          |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 21 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Arthralgia                                      |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 21 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bacteraemia                                     |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 21 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                     | Control         | Sodium Bicarbonate |  |
|-------------------------------------------------------|-----------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                 |                    |  |
| subjects affected / exposed                           | 4 / 22 (18.18%) | 4 / 21 (19.05%)    |  |
| Cardiac disorders                                     |                 |                    |  |
| High blood pressure                                   |                 |                    |  |
| subjects affected / exposed                           | 0 / 22 (0.00%)  | 1 / 21 (4.76%)     |  |
| occurrences (all)                                     | 0               | 1                  |  |
| Gastrointestinal disorders                            |                 |                    |  |
| Gastrointestinal bleeding                             |                 |                    |  |
| subjects affected / exposed                           | 1 / 22 (4.55%)  | 0 / 21 (0.00%)     |  |
| occurrences (all)                                     | 1               | 0                  |  |
| Diverticulitis                                        |                 |                    |  |
| subjects affected / exposed                           | 2 / 22 (9.09%)  | 0 / 21 (0.00%)     |  |
| occurrences (all)                                     | 2               | 0                  |  |
| Infections and infestations                           |                 |                    |  |
| Enterococcus faecalis infection                       |                 |                    |  |
| subjects affected / exposed                           | 1 / 22 (4.55%)  | 0 / 21 (0.00%)     |  |
| occurrences (all)                                     | 1               | 0                  |  |
| Chest infection                                       |                 |                    |  |

|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 3 / 21 (14.29%) |  |
| occurrences (all)           | 0              | 3               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported