



## Clinical trial results:

### Treatment of congenital nephrogenic diabetes insipidus with a guanylate cyclase stimulator, riociguat or a phosphodiesterase type 5 inhibitor, sildenafil

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-001591-30 |
| Trial protocol           | DK             |
| Global end of trial date | 06 June 2019   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 04 June 2020 |
| First version publication date | 04 June 2020 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | S-20150201 |
|-----------------------|------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Claus Bistrup   |
| Sponsor organisation address | J.B. Winsløvs Vej 4, Odense C, Denmark, 5000                                |
| Public contact               | Dept. of Nephrology, Odense University Hospital, 45 65411106, ode.y@rsyd.dk |
| Scientific contact           | Dept. of Nephrology, Odense University Hospital, 45 65411106, ode.y@rsyd.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:

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**Results analysis stage**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 01 November 2019 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 06 June 2019     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 06 June 2019     |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

The aim of the study is to test the hypothesis that treatment with riociguat or sildenafil in patients with NDI caused by AVP2R mutation improves the symptoms by reducing diuresis

Protection of trial subjects:

Patients were hospitalized for the first two days of each intervention to enable close monitoring of side-effects. For the rest of each intervention, patients had daily check-ups where symptoms and side-effects were monitored and handled.

Background therapy:

None

Evidence for comparator:

Not applicable.

The effect of the two interventions was evaluated by comparing baseline values to similar values after each intervention.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 20 February 2019 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Denmark: 2 |
| Worldwide total number of subjects   | 2          |
| EEA total number of subjects         | 2          |

Notes:

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**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)                      | 2 |

|                     |   |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over   | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The two subjects were included on the 20th of February 2019 after oral and written information. Written informed consent was obtained before any study related procedures.

### Pre-assignment

Screening details:

The two subjects fulfilling the eligibility criteria were recruited from the outpatient clinic at the Department of Nephrology, Odense University Hospital.

### Period 1

|                              |                |
|------------------------------|----------------|
| Period 1 title               | Sildenafil     |
| Is this the baseline period? | Yes            |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

### Arms

|           |            |
|-----------|------------|
| Arm title | Sildenafil |
|-----------|------------|

Arm description:

Intervention

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Sildenafil   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

50 mg x 3/day for 7 days

|                                |            |
|--------------------------------|------------|
| Number of subjects in period 1 | Sildenafil |
| Started                        | 2          |
| Completed                      | 2          |

### Period 2

|                              |                |
|------------------------------|----------------|
| Period 2 title               | Riociguat      |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

### Arms

|  |              |
|--|--------------|
| <b>Arm title</b>                       | Riociguat    |
| Arm description: -                     |              |
| Arm type                               | Experimental |
| Investigational medicinal product name | Riociguat    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

1 mg 3 times per day

|                                       |           |
|---------------------------------------|-----------|
| <b>Number of subjects in period 2</b> | Riociguat |
| Started                               | 2         |
| Completed                             | 2         |

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Sildenafil |
|-----------------------|------------|

Reporting group description: -

| Reporting group values                                | Sildenafil     | Total |  |
|---|----------------|-------|--|
| Number of subjects                                    | 2              | 2     |  |
| Age categorical                                       |                |       |  |
| Units: Subjects                                       |                |       |  |
| In utero  | 0              | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0              | 0     |  |
| Newborns (0-27 days)                                  | 0              | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0              | 0     |  |
| Children (2-11 years)                                 | 0              | 0     |  |
| Adolescents (12-17 years)                             | 0              | 0     |  |
| Adults (18-64 years)                                  | 2              | 2     |  |
| From 65-84 years                                      | 0              | 0     |  |
| 85 years and over                                     | 0              | 0     |  |
| Age continuous  |                |       |  |
| Units: years  |                |       |  |
| median  | 28             |       |  |
| full range (min-max)                                  | 28 to 28       | -     |  |
| Gender categorical                                    |                |       |  |
| Units: Subjects                                       |                |       |  |
| Female  | 0              | 0     |  |
| Male  | 2              | 2     |  |
| Bodyweight  |                |       |  |
| Units: kg   |                |       |  |
| arithmetic mean                                       | 143.5          |       |  |
| full range (min-max)                                  | 142.4 to 144.6 | -     |  |
| Height  |                |       |  |
| Units: cm   |                |       |  |
| arithmetic mean                                       | 182.5          |       |  |
| full range (min-max)                                  | 182.5 to 182.5 | -     |  |

## End points

### End points reporting groups

|                                |            |
|--------------------------------|------------|
| Reporting group title          | Sildenafil |
| Reporting group description:   |            |
| Intervention                   |            |
| Reporting group title          | Riociguat  |
| Reporting group description: - |            |

### Primary: Diureses per hour

|                        |                                  |
|------------------------|----------------------------------|
| End point title        | Diureses per hour <sup>[1]</sup> |
| End point description: |                                  |

|                               |         |
|-------------------------------|---------|
| End point type                | Primary |
| End point timeframe:          |         |
| During water deprivation test |         |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: N=2, therefor, no statistic analysis has been performed

| End point values                       | Sildenafil            | Riociguat         |  |  |
|--|-----------------------|-------------------|--|--|
| Subject group type                     | Reporting group       | Reporting group   |  |  |
| Number of subjects analysed            | 2                     | 2                 |  |  |
| Units: mL                              |                       |                   |  |  |
| arithmetic mean (full range (min-max)) | 1103.67 (809 to 1685) | 971 (764 to 1335) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: water intake

|                        |                             |
|------------------------|-----------------------------|
| End point title        | water intake <sup>[2]</sup> |
| End point description: |                             |

|                             |         |
|-----------------------------|---------|
| End point type              | Primary |
| End point timeframe:        |         |
| During intervention periode |         |

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Water intake was not measured. No statistical analysis performed.

| End point values                       | Sildenafil       | Riociguat        |  |  |
|--|------------------|------------------|--|--|
| Subject group type                     | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed            | 2 <sup>[3]</sup> | 2 <sup>[4]</sup> |  |  |
| Units: mL                              |                  |                  |  |  |
| arithmetic mean (full range (min-max)) | 0 (0 to 0)       | 0 (0 to 0)       |  |  |

Notes:

[3] - Not measured

[4] - Not measured

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Diureses per 24h

|                 |                  |
|-----------------|------------------|
| End point title | Diureses per 24h |
|-----------------|------------------|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

During intervention periode

| End point values                       | Sildenafil                     | Riociguat                      |  |  |
|--|--------------------------------|--------------------------------|--|--|
| Subject group type                     | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed            | 2                              | 2                              |  |  |
| Units: mL                              |                                |                                |  |  |
| arithmetic mean (full range (min-max)) | 10817.33<br>(8480 to<br>13320) | 13177.83<br>(9240 to<br>18140) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Urinary osmolality

|                 |                    |
|-----------------|--------------------|
| End point title | Urinary osmolality |
|-----------------|--------------------|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

During intervention period



| <b>End point values</b>                | Sildenafil       | Riociguat        |  |  |
|--|------------------|------------------|--|--|
| Subject group type                     | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed            | 2                | 2                |  |  |
| Units: mosm/kg                         |                  |                  |  |  |
| arithmetic mean (full range (min-max)) | 92.58 (84 to 99) | 88.08 (75 to 98) |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During interventions

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

### Dictionary used

|                 |           |
|-----------------|-----------|
| Dictionary name | SNOMED CT |
|-----------------|-----------|

|                    |        |
|--------------------|--------|
| Dictionary version | 2019AB |
|--------------------|--------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Sildenafil |
|-----------------------|------------|

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | Riociguat |
|-----------------------|-----------|

Reporting group description: -

| Serious adverse events                            | Sildenafil    | Riociguat     |  |
|---|---------------|---------------|--|
| Total subjects affected by serious adverse events |               |               |  |
| subjects affected / exposed                       | 0 / 2 (0.00%) | 0 / 2 (0.00%) |  |
| number of deaths (all causes)                     | 0             | 0             |  |
| number of deaths resulting from adverse events    | 0             | 0             |  |

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

| Non-serious adverse events                            | Sildenafil      | Riociguat       |  |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                 |                 |  |
| subjects affected / exposed                           | 2 / 2 (100.00%) | 2 / 2 (100.00%) |  |
| Vascular disorders                                    |                 |                 |  |
| Flushing  |                 |                 |  |
| subjects affected / exposed                           | 1 / 2 (50.00%)  | 0 / 2 (0.00%)   |  |
| occurrences (all)                                     | 2               | 0               |  |
| Nervous system disorders                              |                 |                 |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                           | 2 / 2 (100.00%) | 1 / 2 (50.00%)  |  |
| occurrences (all)                                     | 2               | 2               |  |
| Gastrointestinal disorders                            |                 |                 |  |
| Gastritis   |                 |                 |  |
| subjects affected / exposed                           | 2 / 2 (100.00%) | 1 / 2 (50.00%)  |  |
| occurrences (all)                                     | 3               | 1               |  |

|  |                                       |                    |  |
|--|---------------------------------------|--------------------|--|
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)                                       | Additional description: Lower abdomen |                    |  |
|  | 1 / 2 (50.00%)<br>1                   | 0 / 2 (0.00%)<br>0 |  |
| Musculoskeletal and connective tissue disorders<br>Myalgia<br>subjects affected / exposed<br>occurrences (all) |                                       |                    |  |
|  | Additional description: Slight        |                    |  |
|  | 2 / 2 (100.00%)<br>2                  | 0 / 2 (0.00%)<br>0 |  |

## 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|                       |
|-----------------------|
| Only two participants |
|-----------------------|

Notes: