



## Clinical trial results:

**Efficacy and safety of bumetanide oral liquid formulation in children and adolescents aged from 7 to less than 18 years old with Autism Spectrum Disorder.**

**A 6-month randomised, double-blind, placebo controlled multicentre parallel group study to evaluate efficacy and safety of bumetanide 0.5mg twice a day followed by an open label active 6-month treatment period with bumetanide (0.5mg twice a day) and a 6 weeks discontinuation period after treatment stop.**

## Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2017-004419-38                      |
| Trial protocol           | GB FR DE ES NL HU PT PL IT IE CZ SK |
| Global end of trial date | 13 September 2021                   |

## Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 20 March 2022 |
| First version publication date | 20 March 2022 |

## Trial information

### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CL3-95008-001 |
|-----------------------|---------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03715166 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Institut de Recherches Internationales Servier   |
| Sponsor organisation address | 50 rue Carnot, Suresnes, France, 92284   |
| Public contact               | Therapeutic Area in Neurology, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com |
| Scientific contact           | Therapeutic Area in Neurology, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com |
| Sponsor organisation name    | Laboratorios Servier SL  |
| Sponsor organisation address | Avenida de los Madronos, 33, Madrid, Spain, 28043  |
| Public contact               | Dpto. de Investigation y Desarrollo, Laboratorios Servier SL, +34 917489662, itziar.martinezmelchor@servier.com          |
| Scientific contact           | Dpto. de Investigation y Desarrollo, Laboratorios Servier SL, +34 917489662, itziar.martinezmelchor@servier.com          |
| Sponsor organisation name    | Servier R&D Ltd  |
| Sponsor organisation address | Sefton House, Sefton Park, Bell Hill, Stoke Poges, Slough, Berkshire, United Kingdom, SL245S                             |
| Public contact               | Institut de Recherches Internationales Servier, Therapeutic  |

|                    |   |
|--------------------|---|
|                    | Area in Neurology, +33 01 55 72 43 66,<br>clinicaltrials@servier.com  |
| Scientific contact | Institut de Recherches Internationales Servier, Therapeutic<br>Area in Neurology, +33 01 55 72 43 66,<br>clinicaltrials@servier.com |

Notes:

### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-001303-PIP01-12 |
| 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                       | 13 September 2021 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 13 September 2021 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 13 September 2021 |
| Was the trial ended prematurely?                     | Yes               |

Notes:

### General information about the trial

Main objective of the trial:

To demonstrate the superiority of bumetanide (0.5 mg b.i.d.) oral liquid formulation compared to placebo in the improvement of ASD core symptoms, as evaluated on Childhood Autism Rating Scale, second edition (CARS2), after 6 months of treatment in ASD children and adolescents aged from 7 to less than 18 years old.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 21 September 2018 |
| 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**

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Brazil: 27         |
| Country: Number of subjects enrolled | France: 23         |
| Country: Number of subjects enrolled | Germany: 5         |
| Country: Number of subjects enrolled | Hungary: 20        |
| Country: Number of subjects enrolled | Italy: 25          |
| Country: Number of subjects enrolled | Netherlands: 1     |
| Country: Number of subjects enrolled | Poland: 26         |
| Country: Number of subjects enrolled | Portugal: 14       |
| Country: Number of subjects enrolled | Spain: 41          |
| Country: Number of subjects enrolled | United Kingdom: 29 |
| Worldwide total number of subjects   | 211                |
| EEA total number of subjects         | 155                |

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)                     | 141 |
| Adolescents (12-17 years)                 | 70  |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Male and female patients from 7 to less than 18 years old.

Primary diagnosis of ASD as per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) , confirmed by Autism Diagnostic Observation Schedule-Generic (ADOS-2) and Autism Diagnosis Interview Revised, Clinical Global Impression Severity (CGI-S) Score  $\geq 4$ , CARS2 total raw score  $\geq 34$ .

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Double-blind period (From W000 to W026) |
| Is this the baseline period? | Yes                                     |
| Allocation method            | Randomised - controlled                 |
| Blinding used                | Double blind                            |
| Roles blinded                | Investigator, Subject                   |

### Arms

|  |                              |
|--|------------------------------|
| Are arms mutually exclusive?           | Yes                          |
| <b>Arm title</b>                       | S95008 - Double-blind period |
| Arm description: -                     |                              |
| Arm type                               | Experimental                 |
| Investigational medicinal product name | S95008                       |
| Investigational medicinal product code | S95008                       |
| Other name                             |                              |
| Pharmaceutical forms                   | Oral solution                |
| Routes of administration               | Oral use                     |

Dosage and administration details:

The IMP dispensed was an oral solution of 0.5 mg/mL of S95008 (bumetanide).

All the patients took orally the study treatment twice a day:

- in the morning at wake up.
- in the afternoon, 3 hours before going to bed at the latest.

The volume of the oral solution was adapted according to a body-weight basis for patients with a weight lower than 25 kg.

|  |                               |
|--|-------------------------------|
| <b>Arm title</b>                       | Placebo - Double-blind period |
| Arm description: -                     |                               |
| Arm type                               | Placebo                       |
| Investigational medicinal product name | Placebo                       |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Oral solution                 |
| Routes of administration               | Oral use                      |

Dosage and administration details:

The IMP dispensed was an oral solution.

All the patients took orally the study treatment twice a day:

- in the morning at wake up.
- in the afternoon, 3 hours before going to bed at the latest.

The volume of the oral solution was adapted according to a body-weight basis for patients with a weight lower than 25 kg.

| Number of subjects in period 1 | S95008 - Double-blind period | Placebo - Double-blind period |
|--------------------------------|------------------------------|-------------------------------|
| Started                        | 107                          | 104                           |
| Completed                      | 89                           | 93                            |
| Not completed                  | 18                           | 11                            |
| Non medical reason             | 10                           | 7                             |
| Adverse event, non-fatal       | 7                            | 3                             |
| Protocol deviation             | 1                            | 1                             |

## Period 2

|                              |                                       |
|------------------------------|---------------------------------------|
| Period 2 title               | Open-label period (From W026 to W052) |
| Is this the baseline period? | No                                    |
| Allocation method            | Non-randomised - controlled           |
| Blinding used                | Not blinded                           |

## Arms

|                              |                                    |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | No                                 |
| <b>Arm title</b>             | Placebo/S95008 - Open-label period |

### Arm description:

Patients assigned to Placebo group at W0 and treated by S95008 in the open-label period.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | S95008        |
| Investigational medicinal product code | S95008        |
| Other name                             |               |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

### Dosage and administration details:

All patients received bumetanide b.i.d. between month 6 (W026) and month 12 (W052).

This was followed by a period from W052 to WEND. During this follow-up period, the patients were not treated with IMP.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | S95008/S95008 - Open label period |
|------------------|-----------------------------------|

### Arm description:

Patients assigned to S95008 group at W0 and treated by S95008 in the open-label period.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | S95008        |
| Investigational medicinal product code | S95008        |
| Other name                             |               |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

### Dosage and administration details:

All patients received bumetanide b.i.d. between month 6 (W026) and month 12 (W052).

This was followed by a period from W052 to WEND. During this follow-up period, the patients were not treated with IMP.

| Number of subjects in period 2 | Placebo/S95008 - Open-label period | S95008/S95008 - Open label period |
|--------------------------------|------------------------------------|-----------------------------------|
| Started                        | 90                                 | 86                                |
| Completed                      | 74                                 | 76                                |
| Not completed                  | 16                                 | 10                                |
| Non medical reason             | 2                                  | 4                                 |
| Adverse event, non-fatal       | 13                                 | 4                                 |
| Lack of efficacy               | 1                                  | -                                 |
| Protocol deviation             | -                                  | 2                                 |

### Period 3

|                              |                                     |
|------------------------------|-------------------------------------|
| Period 3 title               | Combined period (From W000 to W052) |
| Is this the baseline period? | No                                  |
| Allocation method            | Non-randomised - controlled         |
| Blinding used                | Not blinded                         |

### Arms

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | S95008/S95008 - Combined period |
|------------------|---------------------------------|

Arm description:

For the Combined period (Double-blind + Open label periods), treatment group was defined as S95008/S95008 arm: patients assigned to S95008 group at W0 and treated with S95008 in the open-label period.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | S95008        |
| Investigational medicinal product code | S95008        |
| Other name                             |               |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

Dosage and administration details:

All patients received bumetanide b.i.d. between W000 and month 12 (W052).

This was followed by a period from W052 to WEND. During this follow-up period, the patients were not treated with IMP.

| Number of subjects in period 3 | S95008/S95008 - Combined period |
|--------------------------------|---------------------------------|
| Started                        | 86                              |
| Completed                      | 76                              |
| Not completed                  | 10                              |
| Non medical reason             | 4                               |
| Adverse event, non-fatal       | 4                               |
| Protocol deviation             | 2                               |

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**Period 4**

|                              |                                      |
|------------------------------|--------------------------------------|
| Period 4 title               | Extension period (From M000 to M006) |
| Is this the baseline period? | No                                   |
| Allocation method            | Non-randomised - controlled          |
| Blinding used                | Not blinded                          |

**Arms**

|  |                           |
|--|---------------------------|
| <b>Arm title</b>                       | S95008 - Extension period |
| Arm description: -                     |                           |
| Arm type                               | Experimental              |
| Investigational medicinal product name | S95008                    |
| Investigational medicinal product code | S95008                    |
| Other name                             |                           |
| Pharmaceutical forms                   | Oral solution             |
| Routes of administration               | Oral use                  |

## Dosage and administration details:

During the 6-month extension period in open label (from M000 to M006), all patients were treated by bumetanide as done in the open label treatment period.

|   |                           |
|---|---------------------------|
| <b>Number of subjects in period 4<sup>[1]</sup></b> | S95008 - Extension period |
| Started   | 27                        |
| Completed   | 16                        |
| Not completed                                       | 11                        |
| Non medical reason                                  | 11                        |

## Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The extension period was not mandatory.

## Baseline characteristics

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | S95008 - Double-blind period |
|-----------------------|------------------------------|

|                                |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Placebo - Double-blind period |
|-----------------------|-------------------------------|

|                                |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

| Reporting group values    | S95008 - Double-blind period | Placebo - Double-blind period | Total |
|---------------------------|------------------------------|-------------------------------|-------|
| Number of subjects        | 107                          | 104                           | 211   |
| Age categorical           |                              |                               |       |
| Units: Subjects           |                              |                               |       |
| Children (2-11 years)     | 68                           | 73                            | 141   |
| Adolescents (12-17 years) | 39                           | 31                            | 70    |
| Age continuous            |                              |                               |       |
| Units: years              |                              |                               |       |
| arithmetic mean           | 10.5                         | 10.4                          |       |
| standard deviation        | ± 3.0                        | ± 2.9                         | -     |
| Gender categorical        |                              |                               |       |
| Units: Subjects           |                              |                               |       |
| Female                    | 20                           | 17                            | 37    |
| Male                      | 87                           | 87                            | 174   |



## End points

### End points reporting groups

|  |                                    |
|--|------------------------------------|
| Reporting group title  | S95008 - Double-blind period       |
| Reporting group description: -   |                                    |
| Reporting group title  | Placebo - Double-blind period      |
| Reporting group description: -   |                                    |
| Reporting group title  | Placebo/S95008 - Open-label period |
| Reporting group description:   |                                    |
| Patients assigned to Placebo group at W0 and treated by S95008 in the open-label period.   |                                    |
| Reporting group title  | S95008/S95008 - Open label period  |
| Reporting group description:   |                                    |
| Patients assigned to S95008 group at W0 and treated by S95008 in the open-label period.  |                                    |
| Reporting group title  | S95008/S95008 - Combined period    |
| Reporting group description:   |                                    |
| For the Combined period (Double-blind + Open label periods), treatment group was defined as S95008/S95008 arm: patients assigned to S95008 group at W0 and treated with S95008 in the open-label period. |                                    |
| Reporting group title  | S95008 - Extension period          |
| Reporting group description: -   |                                    |

### Primary: CARS2 total raw score: change from baseline to 6 months.

|  |  |
|--|--|
| End point title  | CARS2 total raw score: change from baseline to 6 months. |
| End point description:   |  |
| Its main expression was the change from baseline to 6 months. The primary analysis consisted in the difference between bumetanide and placebo using a general linear model with baseline CARS2 total raw score and stratification factors as covariates. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| CARS2 was completed by an independent rater, who performed a mandatory training before his/her involvement in the study, at W000, W004, W012, W026.  |  |

| End point values                     | S95008 - Double-blind period | Placebo - Double-blind period |  |  |
|--------------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type                   | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed          | 90                           | 93                            |  |  |
| Units: No unit                       |                              |                               |  |  |
| arithmetic mean (standard deviation) | -3.48 (± 4.31)               | -2.96 (± 4.22)                |  |  |

### Statistical analyses

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | S95008 minus Placebo |
|----------------------------|----------------------|

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**Statistical analysis description:**

Bumetanide was compared to placebo on the primary efficacy endpoint (change from baseline to W026 of the CARS2 total score) in the RS, using a General Linear Model including the fixed, categorical effect of treatment, gender and country as well as the continuous fixed covariate of baseline value.

The Estimate of the adjusted difference was based on 211 patients (Data amputation of missing data).

|   |  |
|---|--|
| Comparison groups                       | S95008 - Double-blind period v Placebo - Double-blind period |
| Number of subjects included in analysis | 183  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.455  |
| Method                                  | Two-sided 95% CI of the Estimate                             |
| Parameter estimate                      | Estimate of the adjusted difference                          |
| Point estimate                          | -0.45  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -1.64  |
| upper limit                             | 0.74   |
| Variability estimate                    | Standard error of the mean                                   |
| Dispersion value                        | 0.61   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events which occurred or worsen or became serious according to the investigator, or upgraded by the Sponsor, between the first IMP intake date (included) and the last IMP intake date + 1 day (included) of the considered period.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 24.0   |

### Reporting groups

|                                |                                    |
|--------------------------------|------------------------------------|
| Reporting group title          | S95008 - Double-blind period       |
| Reporting group description: - |                                    |
| Reporting group title          | Placebo - Double-blind period      |
| Reporting group description: - |                                    |
| Reporting group title          | Placebo/S95008 - Open-label period |
| Reporting group description: - |                                    |
| Reporting group title          | S95008/S95008 - Combined period    |
| Reporting group description: - |                                    |
| Reporting group title          | S95008 - Extension period          |
| Reporting group description: - |                                    |

| Serious adverse events                            | S95008 - Double-blind period | Placebo - Double-blind period | Placebo/S95008 - Open-label period |
|---|------------------------------|-------------------------------|------------------------------------|
| Total subjects affected by serious adverse events |                              |                               |                                    |
| subjects affected / exposed                       | 11 / 107 (10.28%)            | 5 / 104 (4.81%)               | 2 / 90 (2.22%)                     |
| number of deaths (all causes)                     | 0                            | 0                             | 0                                  |
| number of deaths resulting from adverse events    | 0                            | 0                             | 0                                  |
| Investigations                                    |                              |                               |                                    |
| Alanine aminotransferase increased                |                              |                               |                                    |
| subjects affected / exposed                       | 0 / 107 (0.00%)              | 1 / 104 (0.96%)               | 0 / 90 (0.00%)                     |
| occurrences causally related to treatment / all   | 0 / 0                        | 0 / 1                         | 0 / 0                              |
| deaths causally related to treatment / all        | 0 / 0                        | 0 / 0                         | 0 / 0                              |
| Aspartate aminotransferase increased              |                              |                               |                                    |
| subjects affected / exposed                       | 0 / 107 (0.00%)              | 1 / 104 (0.96%)               | 0 / 90 (0.00%)                     |
| occurrences causally related to treatment / all   | 0 / 0                        | 0 / 1                         | 0 / 0                              |
| deaths causally related to treatment / all        | 0 / 0                        | 0 / 0                         | 0 / 0                              |
| Blood potassium increased                         |                              |                               |                                    |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 104 (0.96%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Injury, poisoning and procedural complications  |                 |                 |                |
| Forearm fracture                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 104 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nervous system disorders                        |                 |                 |                |
| Epilepsy  |                 |                 |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Febrile convulsion                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Generalised tonic-clonic seizure                |                 |                 |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 1 / 104 (0.96%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypoglycaemic unconsciousness                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 104 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Partial seizures with secondary generalisation  |                 |                 |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Petit mal epilepsy                              |                 |                 |                |
| subjects affected / exposed                     | 2 / 107 (1.87%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| Seizure  |                 |                 |                |
| subjects affected / exposed                          | 0 / 107 (0.00%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Syncope  |                 |                 |                |
| subjects affected / exposed                          | 1 / 107 (0.93%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Tonic convulsion                                     |                 |                 |                |
| subjects affected / exposed                          | 1 / 107 (0.93%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions |                 |                 |                |
| Pyrexia  |                 |                 |                |
| subjects affected / exposed                          | 1 / 107 (0.93%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal disorders                           |                 |                 |                |
| Diarrhoea  |                 |                 |                |
| subjects affected / exposed                          | 1 / 107 (0.93%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                |
| Asthma   |                 |                 |                |
| subjects affected / exposed                          | 1 / 107 (0.93%) | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Bronchospasm   |                 |                 |                |
| subjects affected / exposed                          | 0 / 107 (0.00%) | 1 / 104 (0.96%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Sleep apnoea syndrome                                |                 |                 |                |

|   |                  |                 |                |
|---|------------------|-----------------|----------------|
| subjects affected / exposed                       | 1 / 107 (0.93%)  | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0           | 0 / 0          |
| <b>Psychiatric disorders</b>                      |                  |                 |                |
| Autism spectrum disorder                          |                  |                 |                |
| subjects affected / exposed                       | 1 / 107 (0.93%)  | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0           | 0 / 0          |
| Intentional self-injury                           |                  |                 |                |
| subjects affected / exposed                       | 0 / 107 (0.00%)  | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0           | 0 / 0          |
| <b>Infections and infestations</b>                |                  |                 |                |
| Appendicitis                                      |                  |                 |                |
| subjects affected / exposed                       | 0 / 107 (0.00%)  | 1 / 104 (0.96%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0           | 0 / 0          |
| <b>Metabolism and nutrition disorders</b>         |                  |                 |                |
| Dehydration                                       |                  |                 |                |
| subjects affected / exposed                       | 0 / 107 (0.00%)  | 1 / 104 (0.96%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0            | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0           | 0 / 0          |
| Hypokalaemia                                      |                  |                 |                |
| subjects affected / exposed                       | 2 / 107 (1.87%)  | 0 / 104 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all   | 2 / 2            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0           | 0 / 0          |
| Type 1 diabetes mellitus                          |                  |                 |                |
| subjects affected / exposed                       | 0 / 107 (0.00%)  | 1 / 104 (0.96%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0           | 0 / 0          |
| <b>Serious adverse events</b>                     |                  |                 |                |
| S95008/S95008 - Combined period                   |                  |                 |                |
| S95008 - Extension period                         |                  |                 |                |
| Total subjects affected by serious adverse events |                  |                 |                |
| subjects affected / exposed                       | 10 / 83 (12.05%) | 0 / 27 (0.00%)  |                |
| number of deaths (all causes)                     | 0                | 0               |                |

|   |                |                |  |
|---|----------------|----------------|--|
| number of deaths resulting from adverse events  | 0              | 0              |  |
| Investigations                                  |                |                |  |
| Alanine aminotransferase increased              |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Aspartate aminotransferase increased            |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood potassium increased                       |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Forearm fracture                                |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Epilepsy  |                |                |  |
| subjects affected / exposed                     | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Febrile convulsion                              |                |                |  |
| subjects affected / exposed                     | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Generalised tonic-clonic seizure                |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypoglycaemic unconsciousness                   |                |                |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                          | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Partial seizures with secondary generalisation       |                |                |  |
| subjects affected / exposed                          | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Petit mal epilepsy                                   |                |                |  |
| subjects affected / exposed                          | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Seizure  |                |                |  |
| subjects affected / exposed                          | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Syncope  |                |                |  |
| subjects affected / exposed                          | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Tonic convulsion                                     |                |                |  |
| subjects affected / exposed                          | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Pyrexia  |                |                |  |
| subjects affected / exposed                          | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                           |                |                |  |
| Diarrhoea  |                |                |  |
| subjects affected / exposed                          | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |



|   |                |                |  |
|---|----------------|----------------|--|
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Asthma  |                |                |  |
| subjects affected / exposed                     | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bronchospasm                                    |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sleep apnoea syndrome                           |                |                |  |
| subjects affected / exposed                     | 1 / 83 (1.20%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| Autism spectrum disorder                        |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intentional self-injury                         |                |                |  |
| subjects affected / exposed                     | 1 / 83 (1.20%) | 0 / 27 (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                     |                |                |  |
| Appendicitis                                    |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Dehydration                                     |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypokalaemia                                    |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 2 / 83 (2.41%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Type 1 diabetes mellitus                        |                |                |  |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | S95008 - Double-blind period | Placebo - Double-blind period | Placebo/S95008 - Open-label period |
|---|------------------------------|-------------------------------|------------------------------------|
| Total subjects affected by non-serious adverse events |                              |                               |                                    |
| subjects affected / exposed                           | 97 / 107 (90.65%)            | 84 / 104 (80.77%)             | 77 / 90 (85.56%)                   |
| Investigations  |                              |                               |                                    |
| Urine calcium increased                               |                              |                               |                                    |
| subjects affected / exposed                           | 5 / 107 (4.67%)              | 0 / 104 (0.00%)               | 1 / 90 (1.11%)                     |
| occurrences (all)                                     | 5                            | 0                             | 1                                  |
| Weight decreased                                      |                              |                               |                                    |
| subjects affected / exposed                           | 10 / 107 (9.35%)             | 1 / 104 (0.96%)               | 5 / 90 (5.56%)                     |
| occurrences (all)                                     | 13                           | 1                             | 7                                  |
| Weight increased                                      |                              |                               |                                    |
| subjects affected / exposed                           | 9 / 107 (8.41%)              | 9 / 104 (8.65%)               | 2 / 90 (2.22%)                     |
| occurrences (all)                                     | 13                           | 9                             | 3                                  |
| Nervous system disorders                              |                              |                               |                                    |
| Disturbance in attention                              |                              |                               |                                    |
| subjects affected / exposed                           | 3 / 107 (2.80%)              | 4 / 104 (3.85%)               | 0 / 90 (0.00%)                     |
| occurrences (all)                                     | 3                            | 4                             | 0                                  |
| Headache  |                              |                               |                                    |
| subjects affected / exposed                           | 9 / 107 (8.41%)              | 12 / 104 (11.54%)             | 6 / 90 (6.67%)                     |
| occurrences (all)                                     | 14                           | 17                            | 8                                  |
| General disorders and administration site conditions  |                              |                               |                                    |
| Fatigue   |                              |                               |                                    |
| subjects affected / exposed                           | 12 / 107 (11.21%)            | 12 / 104 (11.54%)             | 6 / 90 (6.67%)                     |
| occurrences (all)                                     | 13                           | 13                            | 6                                  |
| Pyrexia   |                              |                               |                                    |

|   |                         |                         |                        |
|---|-------------------------|-------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                    | 8 / 107 (7.48%)<br>9    | 7 / 104 (6.73%)<br>10   | 11 / 90 (12.22%)<br>13 |
| Thirst<br>subjects affected / exposed<br>occurrences (all)          | 50 / 107 (46.73%)<br>59 | 31 / 104 (29.81%)<br>32 | 36 / 90 (40.00%)<br>40 |
| Gastrointestinal disorders  |                         |                         |                        |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)  | 6 / 107 (5.61%)<br>7    | 8 / 104 (7.69%)<br>8    | 7 / 90 (7.78%)<br>10   |
| Constipation<br>subjects affected / exposed<br>occurrences (all)    | 6 / 107 (5.61%)<br>6    | 1 / 104 (0.96%)<br>1    | 2 / 90 (2.22%)<br>2    |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)       | 13 / 107 (12.15%)<br>22 | 13 / 104 (12.50%)<br>16 | 4 / 90 (4.44%)<br>5    |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)       | 24 / 107 (22.43%)<br>24 | 14 / 104 (13.46%)<br>15 | 14 / 90 (15.56%)<br>15 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)          | 5 / 107 (4.67%)<br>7    | 7 / 104 (6.73%)<br>10   | 4 / 90 (4.44%)<br>6    |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)        | 8 / 107 (7.48%)<br>11   | 7 / 104 (6.73%)<br>12   | 10 / 90 (11.11%)<br>12 |
| Skin and subcutaneous tissue disorders                              |                         |                         |                        |
| Acne<br>subjects affected / exposed<br>occurrences (all)            | 4 / 107 (3.74%)<br>4    | 7 / 104 (6.73%)<br>7    | 2 / 90 (2.22%)<br>3    |
| Psychiatric disorders   |                         |                         |                        |
| Affect lability<br>subjects affected / exposed<br>occurrences (all) | 5 / 107 (4.67%)<br>8    | 3 / 104 (2.88%)<br>3    | 1 / 90 (1.11%)<br>1    |
| Aggression<br>subjects affected / exposed<br>occurrences (all)      | 4 / 107 (3.74%)<br>6    | 5 / 104 (4.81%)<br>6    | 6 / 90 (6.67%)<br>7    |
| Anger   |                         |                         |                        |

|  |                         |                         |                        |
|--|-------------------------|-------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)   | 8 / 107 (7.48%)<br>9    | 3 / 104 (2.88%)<br>4    | 1 / 90 (1.11%)<br>2    |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                    | 8 / 107 (7.48%)<br>10   | 7 / 104 (6.73%)<br>7    | 4 / 90 (4.44%)<br>4    |
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)                             | 4 / 107 (3.74%)<br>4    | 3 / 104 (2.88%)<br>5    | 1 / 90 (1.11%)<br>1    |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                   | 5 / 107 (4.67%)<br>6    | 4 / 104 (3.85%)<br>4    | 0 / 90 (0.00%)<br>0    |
| Irritability<br>subjects affected / exposed<br>occurrences (all)                               | 9 / 107 (8.41%)<br>10   | 10 / 104 (9.62%)<br>12  | 5 / 90 (5.56%)<br>7    |
| Renal and urinary disorders<br>Pollakiuria<br>subjects affected / exposed<br>occurrences (all) | 12 / 107 (11.21%)<br>13 | 2 / 104 (1.92%)<br>2    | 7 / 90 (7.78%)<br>8    |
| Polyuria<br>subjects affected / exposed<br>occurrences (all)                                   | 29 / 107 (27.10%)<br>31 | 12 / 104 (11.54%)<br>12 | 19 / 90 (21.11%)<br>21 |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all)    | 0 / 107 (0.00%)<br>0    | 0 / 104 (0.00%)<br>0    | 5 / 90 (5.56%)<br>5    |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                                  | 6 / 107 (5.61%)<br>6    | 5 / 104 (4.81%)<br>5    | 1 / 90 (1.11%)<br>1    |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                            | 13 / 107 (12.15%)<br>17 | 5 / 104 (4.81%)<br>6    | 8 / 90 (8.89%)<br>11   |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                   | 3 / 107 (2.80%)<br>3    | 2 / 104 (1.92%)<br>2    | 2 / 90 (2.22%)<br>4    |
| Metabolism and nutrition disorders   |                         |                         |                        |

|  |                         |                       |                        |
|--|-------------------------|-----------------------|------------------------|
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 21 / 107 (19.63%)<br>21 | 8 / 104 (7.69%)<br>10 | 3 / 90 (3.33%)<br>3    |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)       | 20 / 107 (18.69%)<br>27 | 4 / 104 (3.85%)<br>5  | 16 / 90 (17.78%)<br>23 |
| Increased appetite<br>subjects affected / exposed<br>occurrences (all) | 17 / 107 (15.89%)<br>20 | 9 / 104 (8.65%)<br>9  | 4 / 90 (4.44%)<br>4    |

| <b>Non-serious adverse events</b>   | S95008/S95008 -<br>Combined period | S95008 - Extension<br>period |  |
|---|------------------------------------|------------------------------|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 82 / 83 (98.80%)                   | 10 / 27 (37.04%)             |  |
| Investigations  |                                    |                              |  |
| Urine calcium increased<br>subjects affected / exposed<br>occurrences (all)             | 5 / 83 (6.02%)<br>7                | 0 / 27 (0.00%)<br>0          |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                    | 9 / 83 (10.84%)<br>14              | 0 / 27 (0.00%)<br>0          |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                    | 12 / 83 (14.46%)<br>21             | 0 / 27 (0.00%)<br>0          |  |
| Nervous system disorders  |                                    |                              |  |
| Disturbance in attention<br>subjects affected / exposed<br>occurrences (all)            | 5 / 83 (6.02%)<br>6                | 0 / 27 (0.00%)<br>0          |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                            | 9 / 83 (10.84%)<br>19              | 2 / 27 (7.41%)<br>2          |  |
| General disorders and administration<br>site conditions                                 |                                    |                              |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                             | 9 / 83 (10.84%)<br>11              | 1 / 27 (3.70%)<br>1          |  |
| Pyrexia   |                                    |                              |  |

|  |                  |                |  |
|--|------------------|----------------|--|
| subjects affected / exposed            | 12 / 83 (14.46%) | 0 / 27 (0.00%) |  |
| occurrences (all)                      | 14               | 0              |  |
| Thirst                                 |                  |                |  |
| subjects affected / exposed            | 47 / 83 (56.63%) | 0 / 27 (0.00%) |  |
| occurrences (all)                      | 69               | 0              |  |
| Gastrointestinal disorders             |                  |                |  |
| Abdominal pain                         |                  |                |  |
| subjects affected / exposed            | 11 / 83 (13.25%) | 1 / 27 (3.70%) |  |
| occurrences (all)                      | 17               | 1              |  |
| Constipation                           |                  |                |  |
| subjects affected / exposed            | 6 / 83 (7.23%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                      | 6                | 0              |  |
| Diarrhoea                              |                  |                |  |
| subjects affected / exposed            | 11 / 83 (13.25%) | 1 / 27 (3.70%) |  |
| occurrences (all)                      | 22               | 1              |  |
| Dry mouth                              |                  |                |  |
| subjects affected / exposed            | 22 / 83 (26.51%) | 0 / 27 (0.00%) |  |
| occurrences (all)                      | 29               | 0              |  |
| Nausea                                 |                  |                |  |
| subjects affected / exposed            | 6 / 83 (7.23%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                      | 8                | 0              |  |
| Vomiting                               |                  |                |  |
| subjects affected / exposed            | 8 / 83 (9.64%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                      | 13               | 0              |  |
| Skin and subcutaneous tissue disorders |                  |                |  |
| Acne                                   |                  |                |  |
| subjects affected / exposed            | 6 / 83 (7.23%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                      | 6                | 0              |  |
| Psychiatric disorders                  |                  |                |  |
| Affect lability                        |                  |                |  |
| subjects affected / exposed            | 6 / 83 (7.23%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                      | 10               | 0              |  |
| Aggression                             |                  |                |  |
| subjects affected / exposed            | 2 / 83 (2.41%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                      | 3                | 0              |  |
| Anger                                  |                  |                |  |

|                                    |                  |                |  |
|------------------------------------|------------------|----------------|--|
| subjects affected / exposed        | 7 / 83 (8.43%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                  | 8                | 0              |  |
| Anxiety                            |                  |                |  |
| subjects affected / exposed        | 7 / 83 (8.43%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                  | 13               | 0              |  |
| Depressed mood                     |                  |                |  |
| subjects affected / exposed        | 6 / 83 (7.23%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                  | 6                | 0              |  |
| Insomnia                           |                  |                |  |
| subjects affected / exposed        | 9 / 83 (10.84%)  | 0 / 27 (0.00%) |  |
| occurrences (all)                  | 11               | 0              |  |
| Irritability                       |                  |                |  |
| subjects affected / exposed        | 10 / 83 (12.05%) | 0 / 27 (0.00%) |  |
| occurrences (all)                  | 13               | 0              |  |
| Renal and urinary disorders        |                  |                |  |
| Pollakiuria                        |                  |                |  |
| subjects affected / exposed        | 9 / 83 (10.84%)  | 0 / 27 (0.00%) |  |
| occurrences (all)                  | 11               | 0              |  |
| Polyuria                           |                  |                |  |
| subjects affected / exposed        | 28 / 83 (33.73%) | 1 / 27 (3.70%) |  |
| occurrences (all)                  | 32               | 1              |  |
| Infections and infestations        |                  |                |  |
| COVID-19                           |                  |                |  |
| subjects affected / exposed        | 4 / 83 (4.82%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                  | 4                | 0              |  |
| Influenza                          |                  |                |  |
| subjects affected / exposed        | 7 / 83 (8.43%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                  | 7                | 0              |  |
| Nasopharyngitis                    |                  |                |  |
| subjects affected / exposed        | 17 / 83 (20.48%) | 1 / 27 (3.70%) |  |
| occurrences (all)                  | 25               | 1              |  |
| Rhinitis                           |                  |                |  |
| subjects affected / exposed        | 6 / 83 (7.23%)   | 0 / 27 (0.00%) |  |
| occurrences (all)                  | 6                | 0              |  |
| Metabolism and nutrition disorders |                  |                |  |

|                             |                  |                 |  |
|-----------------------------|------------------|-----------------|--|
| Decreased appetite          |                  |                 |  |
| subjects affected / exposed | 18 / 83 (21.69%) | 0 / 27 (0.00%)  |  |
| occurrences (all)           | 18               | 0               |  |
| Hypokalaemia                |                  |                 |  |
| subjects affected / exposed | 22 / 83 (26.51%) | 3 / 27 (11.11%) |  |
| occurrences (all)           | 34               | 7               |  |
| Increased appetite          |                  |                 |  |
| subjects affected / exposed | 16 / 83 (19.28%) | 0 / 27 (0.00%)  |  |
| occurrences (all)           | 20               | 0               |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 16 May 2018      | -Amendment No. 1 applicable in all countries, concerned the addition of the mention that additional pregnancy tests could be performed during the study according to local regulations and/or if the medical doctor deemed them as necessary and the update of the potassium supplementation recommendations in case of hypokalaemia. |
| 12 December 2018 | -Amendment No. 2 applicable in all countries, mainly aimed to clarify the investigation schedule and to update some non-selection, exclusion and withdrawal criteria.   |
| 12 August 2019   | -Amendment No. 3, applicable in all countries, aimed to update the exclusion and the withdrawal criteria, about abnormal urinary calcium/creatinine ratio and calciuria.  |
| 30 November 2020 | -Amendment No. 9, applicable in all countries, aimed to update the definition of the end of the trial as a 6-month extension period in open-label was performed in 3 countries.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date              | Interruption  | Restart date |
|-------------------|---|--------------|
| 13 September 2021 | The superiority of bumetanide compared to placebo in ASD was not demonstrated in this phase III study. As none of the efficacy endpoints were reached and due to the identified risk of hypokalaemia and associated effects linked to the drug's diuretic activity, the Benefit/Risk ratio of the study treatment in ASD was considered negative. Consequently, the sponsor decided to stop the S95008 development and prematurely discontinue the extension period. This decision was not related to unexpected safety concerns. | -            |

Notes:

### Limitations and caveats

None reported