



## Clinical trial results:

**Pilot Trial to preserve residual insulin secretion in children and adolescents with recent onset Type 1 diabetes by using GAD-antigen (Diamyd) therapy in combination with Vitamin D and Ibuprofen .**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-003251-11   |
| Trial protocol           | SE               |
| Global end of trial date | 30 November 2016 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 14 June 2017 |
| First version publication date | 14 June 2017 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | DIABGAD-1 |
|-----------------------|-----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |                                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Div of Pediatrics, Dept of Clinical and Experimental Medicine, Faculty of Health Medicine |
| Sponsor organisation address | Linköping University, Linköping, Sweden, SE-581 85                                        |
| Public contact               | Johnny Ludvigsson, Linköping University, 46 13286854, Johnny.Ludvigsson@liu.se            |
| Scientific contact           | Johnny Ludvigsson, Linköping University, 46 13286854, Johnny.Ludvigsson@liu.se            |

Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 30 November 2016 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 30 November 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 November 2016 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

- Evaluate the safety and influence of treatment with GAD-Alum (Diamyd) plus Vitamin D plus Ibuprofen on preservation of residual insulin secretion in recently-diagnosed Type 1 diabetes.
- Evaluate how the abovementioned treatments influences the immune system of the patients and interact with any viral infections.
- Evaluate the safety and influence of treatment with double dose of GAD-Alum (Diamyd) plus Vitamin D on the immune system, viral infections and on preservation of residual insulin secretion in recently-diagnosed Type 1 diabetes

Protection of trial subjects:

After the injection of GAD-Alum (Diamyd)/Placebo at Visit 3 and 4, the patient was to remain in the vicinity of the study site for the next hour, and the injection site were examined by investigator/study nurse 1 hour post injection.

Background therapy:

Standard insulin treatment, education and psycho-social support for newly diagnosed Type 1 diabetes patients. All patients will continue to receive standard care for Type 1 diabetes during the study.

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 04 February 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Sweden: 64 |
| Worldwide total number of subjects   | 64         |
| EEA total number of subjects         | 64         |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 17 |
| Adolescents (12-17 years) | 47 |
| Adults (18-64 years)      | 0  |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from January 2013 to May 2014. Patients were recruited at 9 hospitals in Sweden.

### Pre-assignment

Screening details:

Patients aged 10.00 to 17.99 years at the time of screening and with Type 1 diabetes according to the ADA classification with < 4 months diabetes duration at time of screening.

### Period 1

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

### Arms

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

Arm description:

Patients will be assigned to receive Ibuprofen as oral suspension; 400 mg every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd).

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | D-vitamin Oil |
| Investigational medicinal product code |               |
| Other name                             | Calciferol    |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

Dosage and administration details:

The commercially available Vitamin D, calciferol. Vitamin D was administered as oral solution ; 2000 IU per day (i.e. 25 drops per day) from Day 1 through Day 450.

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Ibuprofen       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Oral suspension |
| Routes of administration               | Oral use        |

Dosage and administration details:

The commercially available ibuprofen.

Ibuprofen was administered as oral suspension; 400 mg every morning from Day 1 through 90.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group B |
|------------------|---------|

Arm description:

Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd).

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |               |
|----------------------------------------|---------------|
| Investigational medicinal product name | D-vitamin Oil |
| Investigational medicinal product code |               |
| Other name                             | Calciferol    |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

**Dosage and administration details:**

The commercially available Vitamin D, calciferol. Vitamin D was administered as oral solution ; 2000 IU per day (i.e. 25 drops per day) from Day 1 through Day 450.

|                                        |                   |
|----------------------------------------|-------------------|
| Investigational medicinal product name | Placebo Ibuprofen |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Oral suspension   |
| Routes of administration               | Oral use          |

**Dosage and administration details:**

Placebo ibuprofen was administered as oral suspension; every morning from Day 1 through 90.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group C |
|------------------|---------|

**Arm description:**

Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 2 subcutaneous injections with 20 µg Diamyd given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster doses (providing a total dose of 80µg Diamyd).

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | D-vitamin Oil |
| Investigational medicinal product code |               |
| Other name                             | Calciferol    |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

**Dosage and administration details:**

The commercially available Vitamin D, calciferol. Vitamin D was administered as oral solution ; 2000 IU per day (i.e. 25 drops per day) from Day 1 through Day 450.

|                                        |                   |
|----------------------------------------|-------------------|
| Investigational medicinal product name | Placebo Ibuprofen |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Oral suspension   |
| Routes of administration               | Oral use          |

**Dosage and administration details:**

Placebo ibuprofen was administered as oral suspension; every morning from Day 1 through 90.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group D |
|------------------|---------|

**Arm description:**

Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and placebo oral drops from Day 1 through 450, and 2 subcutaneous injections with placebo (given at two different sites in the stomach area), each on Days 15 and 45

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Placebo               |
| Investigational medicinal product name | Placebo D-vitamin Oil |
| Investigational medicinal product code |                       |
| Other name                             | Calciferol            |
| Pharmaceutical forms                   | Oral solution         |
| Routes of administration               | Oral use              |

**Dosage and administration details:**

Placebo was administered as oral solution i.e. 25 drops per day from Day 1 through Day 450.

|                                        |                   |
|----------------------------------------|-------------------|
| Investigational medicinal product name | Placebo Ibuprofen |
| Investigational medicinal product code |                   |
| Other name                             |                   |

|                          |                 |
|--------------------------|-----------------|
| Pharmaceutical forms     | Oral suspension |
| Routes of administration | Oral use        |

Dosage and administration details:

Placebo ibuprofen was administered as oral suspension; every morning from Day 1 through 90.

| Number of subjects in period 1 | Group A | Group B | Group C |
|--------------------------------|---------|---------|---------|
| Started                        | 16      | 16      | 16      |
| Completed                      | 16      | 16      | 16      |

| Number of subjects in period 1 | Group D |
|--------------------------------|---------|
| Started                        | 16      |
| Completed                      | 16      |

## Period 2

|                              |                                                 |
|------------------------------|-------------------------------------------------|
| Period 2 title               | Baseline to Month 30                            |
| Is this the baseline period? | No                                              |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Assessor |

Blinding implementation details:

The treatment code was broken 24 March 2015, and data from Visit 1 to Visit 6 (6 months) were made available to one representative from the Sponsor (unblinded statistician), and the drug supplier (Diamyd Medical). The study was kept blinded to patients, investigators and study personnel until study completion.

## Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| Arm title                    | Group A |

Arm description:

Patients will be assigned to receive Ibuprofen as oral suspension; 400 mg every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd).

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | D-vitamin Oil |
| Investigational medicinal product code |               |
| Other name                             | Calciferol    |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

Dosage and administration details:  
The commercially available Vitamin D, calciferol. Vitamin D was administered as oral solution ; 2000 IU per day (i.e. 25 drops per day) from Day 1 through Day 450.

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Ibuprofen       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Oral suspension |
| Routes of administration               | Oral use        |

Dosage and administration details:  
The commercially available ibuprofen.  
Ibuprofen was administered as oral suspension; 400 mg every morning from Day 1 through 90.

|                                        |                          |
|----------------------------------------|--------------------------|
| Investigational medicinal product name | Diamyd                   |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Subcutaneous use         |

Dosage and administration details:  
1 x Diamyd injection.  
Diamyd 20 µg was administered as subcutaneous injections on Days 15 and 45 (prime and booster dose).  
The Diamyd® Drug Product was composed of the rhGAD65 protein formulated in a sterile, non-pyrogenic phosphate buffered saline containing the aluminum hydroxide adjuvant, Alhydrogel®. Diamyd® was administered as a 0.5 mL subcutaneous injection.  
Each injection contained 20 µg Diamyd® protein.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Placebo Diamyd         |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:  
1 x Diamyd placebo injection containing 0 ug Diamyd.  
Diamyd placebo was administered as subcutaneous injections on Days 15 and 45 (prime and booster dose).  
A sterile, non-pyrogenic phosphate buffered saline containing the aluminum hydroxide adjuvant, Alhydrogel®. 0.5 mL subcutaneous injection.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group B |
|------------------|---------|

Arm description:  
Patients will be assigned to receive placebo ibuprofen as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd).

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | D-vitamin Oil |
| Investigational medicinal product code |               |
| Other name                             | Calciferol    |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

Dosage and administration details:  
The commercially available Vitamin D, calciferol. Vitamin D was administered as oral solution ; 2000 IU per day (i.e. 25 drops per day) from Day 1 through Day 450.

|                                        |                   |
|----------------------------------------|-------------------|
| Investigational medicinal product name | Placebo Ibuprofen |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Oral suspension   |
| Routes of administration               | Oral use          |

|                                                                                             |                          |
|---------------------------------------------------------------------------------------------|--------------------------|
| Dosage and administration details:                                                          |                          |
| Placebo ibuprofen was administered as oral suspension; every morning from Day 1 through 90. |                          |
| Investigational medicinal product name                                                      | Diamyd                   |
| Investigational medicinal product code                                                      |                          |
| Other name                                                                                  |                          |
| Pharmaceutical forms                                                                        | Suspension for injection |
| Routes of administration                                                                    | Subcutaneous use         |

Dosage and administration details:

1 x Diamyd injection.

Diamyd 20 µg was administered as subcutaneous injections on Days 15 and 45 (prime and booster dose).

The Diamyd® Drug Product was composed of the rhGAD65 protein formulated in a sterile, non-pyrogenic phosphate buffered saline containing the aluminum hydroxide adjuvant, Alhydrogel®.

Diamyd® was administered as a 0.5 mL subcutaneous injection.

Each injection contained 20 µg Diamyd® protein.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Placebo Diamyd         |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

1 x Diamyd placebo injection containing 0 ug Diamyd.

Diamyd placebo was administered as subcutaneous injections on Days 15 and 45 (prime and booster dose).

A sterile, non-pyrogenic phosphate buffered saline containing the aluminum hydroxide adjuvant, Alhydrogel®. 0.5 mL subcutaneous injection.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group C |
|------------------|---------|

Arm description:

Patients will be assigned to receive placebo ibuprofen as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 2 subcutaneous injections with 20 µg Diamyd given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster doses (providing a total dose of 80µg Diamyd).

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | Placebo Ibuprofen |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Oral suspension   |
| Routes of administration               | Oral use          |

Dosage and administration details:

Placebo ibuprofen was administered as oral suspension; every morning from Day 1 through 90.

|                                        |               |
|----------------------------------------|---------------|
| Investigational medicinal product name | D-vitamin Oil |
| Investigational medicinal product code |               |
| Other name                             | Calciferol    |
| Pharmaceutical forms                   | Oral solution |
| Routes of administration               | Oral use      |

Dosage and administration details:

The commercially available Vitamin D, calciferol. Vitamin D was administered as oral solution ; 2000 IU per day (i.e. 25 drops per day) from Day 1 through Day 450.

|                                        |                          |
|----------------------------------------|--------------------------|
| Investigational medicinal product name | Diamyd                   |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Subcutaneous use         |

Dosage and administration details:

1 x Diamyd injection.

Diamyd 20 µg was administered as subcutaneous injections, on Days 15 and 45 (prime and booster dose).

The Diamyd® Drug Product was composed of the rhGAD65 protein formulated in a sterile, non-pyrogenic phosphate buffered saline containing the aluminum hydroxide adjuvant, Alhydrogel®.

Diamyd® was administered as a 0.5 mL subcutaneous injection.

Each injection contained 20 µg Diamyd® protein.

|                                        |                          |
|----------------------------------------|--------------------------|
| Investigational medicinal product name | Diamyd                   |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Subcutaneous use         |

Dosage and administration details:

1 x Diamyd injection.

Diamyd 20 µg was administered as subcutaneous injections on Days 15 and 45 (prime and booster dose).

The Diamyd® Drug Product was composed of the rhGAD65 protein formulated in a sterile, non-pyrogenic phosphate buffered saline containing the aluminum hydroxide adjuvant, Alhydrogel®.

Diamyd® was administered as a 0.5 mL subcutaneous injection.

Each injection contained 20 µg Diamyd® protein.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group D |
|------------------|---------|

Arm description:

Patients will be assigned to receive placebo ibuprofen as oral suspension every morning from Day 1 through 90 and placebo oral drops from Day 1 through 450, and 2 subcutaneous injections with placebo (given at two different sites in the stomach area), each on Days 15 and 45

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Placebo           |
| Investigational medicinal product name | Placebo Ibuprofen |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Oral suspension   |
| Routes of administration               | Oral use          |

Dosage and administration details:

Placebo ibuprofen was administered as oral suspension; every morning from Day 1 through 90.

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Placebo D-vitamin Oil |
| Investigational medicinal product code |                       |
| Other name                             | Calciferol            |
| Pharmaceutical forms                   | Oral solution         |
| Routes of administration               | Oral use              |

Dosage and administration details:

Placebo was administered as oral solution i.e. 25 drops per day from Day 1 through Day 450.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Placebo Diamyd         |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

1 x Diamyd placebo injection containing 0 ug Diamyd.

Diamyd placebo was administered as subcutaneous injections on Days 15 and 45 (prime and booster dose).

A sterile, non-pyrogenic phosphate buffered saline containing the aluminum hydroxide adjuvant, Alhydrogel®. 0.5 mL subcutaneous injection.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Placebo Diamyd         |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

---

**Dosage and administration details:**

1 x Diamyd placebo injection containing 0 ug Diamyd.

Diamyd placebo was administered as subcutaneous injections on Days 15 and 45 (prime and booster dose).

A sterile, non-pyrogenic phosphate buffered saline containing the aluminum hydroxide adjuvant, Alhydrogel®. 0.5 mL subcutaneous injection.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Group A | Group B | Group C |
|-----------------------------------------------------|---------|---------|---------|
| Started                                             | 16      | 16      | 16      |
| Prime injection Diamyd/Placebo                      | 16      | 16      | 16      |
| Boost injection Diamyd/Placebo                      | 16      | 16      | 15      |
| Completed 6 month visit                             | 16      | 16      | 15      |
| Completed 15 month visit                            | 15      | 16      | 15      |
| Completed 30 month visit                            | 15      | 16      | 15      |
| Completed                                           | 15      | 16      | 15      |
| Not completed                                       | 1       | 0       | 1       |
| Consent withdrawn by subject                        | 1       | -       | 1       |
| Physician decision                                  | -       | -       | -       |

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Group D |
|-----------------------------------------------------|---------|
| Started                                             | 15      |
| Prime injection Diamyd/Placebo                      | 15      |
| Boost injection Diamyd/Placebo                      | 15      |
| Completed 6 month visit                             | 13      |
| Completed 15 month visit                            | 13      |
| Completed 30 month visit                            | 13      |
| Completed                                           | 13      |
| Not completed                                       | 2       |
| Consent withdrawn by subject                        | 1       |
| Physician decision                                  | 1       |

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**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: 1 patient in Group D completed Baseline but decided not to continue in the study after baseline visit.

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                       | Group A |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                |         |
| Patients will be assigned to receive Ibuprofen as oral suspension; 400 mg every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd). |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                       | Group B |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                |         |
| Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd).           |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                       | Group C |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                |         |
| Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 2 subcutaneous injections with 20 µg Diamyd given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster doses (providing a total dose of 80µg Diamyd).                               |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                       | Group D |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                |         |
| Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and placebo oral drops from Day 1 through 450, and 2 subcutaneous injections with placebo (given at two different sites in the stomach area), each on Days 15 and 45                                                                                                                                                                    |         |

| Reporting group values                             | Group A | Group B | Group C |
|----------------------------------------------------|---------|---------|---------|
| Number of subjects                                 | 16      | 16      | 16      |
| Age categorical                                    |         |         |         |
| Units: Subjects                                    |         |         |         |
| In utero                                           | 0       | 0       | 0       |
| Preterm newborn infants (gestational age < 37 wks) | 0       | 0       | 0       |
| Newborns (0-27 days)                               | 0       | 0       | 0       |
| Infants and toddlers (28 days-23 months)           | 0       | 0       | 0       |
| Children (2-11 years)                              | 5       | 4       | 6       |
| Adolescents (12-17 years)                          | 11      | 12      | 10      |
| Adults (18-64 years)                               | 0       | 0       | 0       |
| From 65-84 years                                   | 0       | 0       | 0       |
| 85 years and over                                  | 0       | 0       | 0       |
| Age continuous                                     |         |         |         |
| Units: years                                       |         |         |         |
| arithmetic mean                                    | 13.3    | 14.4    | 13.3    |
| standard deviation                                 | ± 1.9   | ± 2.7   | ± 2.4   |
| Gender categorical                                 |         |         |         |
| Units: Subjects                                    |         |         |         |
| Female                                             | 6       | 7       | 10      |
| Male                                               | 10      | 9       | 6       |

| Reporting group values                                | Group D | Total |  |
|-------------------------------------------------------|---------|-------|--|
| Number of subjects                                    | 16      | 64    |  |
| Age categorical<br>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)                                 | 2       | 17    |  |
| Adolescents (12-17 years)                             | 14      | 47    |  |
| Adults (18-64 years)                                  | 0       | 0     |  |
| From 65-84 years                                      | 0       | 0     |  |
| 85 years and over                                     | 0       | 0     |  |
| Age continuous<br>Units: years                        |         |       |  |
| arithmetic mean                                       | 14.2    |       |  |
| standard deviation                                    | ± 2.2   | -     |  |
| Gender categorical<br>Units: Subjects                 |         |       |  |
| Female                                                | 9       | 32    |  |
| Male                                                  | 7       | 32    |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Group A |
| Reporting group description:<br>Patients will be assigned to receive Ibuprofen as oral suspension; 400 mg every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd). |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Group B |
| Reporting group description:<br>Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd).           |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Group C |
| Reporting group description:<br>Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 2 subcutaneous injections with 20 µg Diamyd given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster doses (providing a total dose of 80µg Diamyd).                               |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Group D |
| Reporting group description:<br>Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and placebo oral drops from Day 1 through 450, and 2 subcutaneous injections with placebo (given at two different sites in the stomach area), each on Days 15 and 45                                                                                                                                                                    |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Group A |
| Reporting group description:<br>Patients will be assigned to receive Ibuprofen as oral suspension; 400 mg every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd). |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Group B |
| Reporting group description:<br>Patients will be assigned to receive placebo ibuprofen as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd). |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Group C |
| Reporting group description:<br>Patients will be assigned to receive placebo ibuprofen as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 2 subcutaneous injections with 20 µg Diamyd given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster doses (providing a total dose of 80µg Diamyd).                     |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Group D |
| Reporting group description:<br>Patients will be assigned to receive placebo ibuprofen as oral suspension every morning from Day 1 through 90 and placebo oral drops from Day 1 through 450, and 2 subcutaneous injections with placebo (given at two different sites in the stomach area), each on Days 15 and 45                                                                                                                                                          |         |

**Primary: Change in AUC for C-peptide from baseline to month 6**

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Change in AUC for C-peptide from baseline to month 6 <sup>[1]</sup> |
|-----------------|---------------------------------------------------------------------|

End point description:

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

End point timeframe:

From baseline to 6 months

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: The clinical study protocol defined statistical methods for efficacy data regarding C-peptide and immune system as well as Adverse events and other safety data as being composed of summary tables with descriptive statistics.

| End point values                     | Group A          | Group B          | Group C         | Group D         |
|--------------------------------------|------------------|------------------|-----------------|-----------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group | Reporting group |
| Number of subjects analysed          | 11               | 15               | 14              | 10              |
| Units: AUC for C-peptide (nmol/L     |                  |                  |                 |                 |
| arithmetic mean (standard deviation) | -0.264 (± 0.231) | -0.114 (± 0.164) | -0.19 (± 0.161) | 0.008 (± 0.271) |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Change in AUC for C-peptide from baseline to month 15**

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Change in AUC for C-peptide from baseline to month 15 <sup>[2]</sup> |
|-----------------|----------------------------------------------------------------------|

End point description:

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

End point timeframe:

From baseline to Month 15

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: The clinical study protocol defined statistical methods for efficacy data regarding C-peptide and immune system as well as Adverse events and other safety data as being composed of summary tables with descriptive statistics.

| End point values                     | Group A          | Group B          | Group C          | Group D          |
|--------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed          | 11               | 15               | 14               | 10               |
| Units: AUC for C-peptide (nmol/L)    |                  |                  |                  |                  |
| arithmetic mean (standard deviation) | -0.362 (± 0.243) | -0.195 (± 0.167) | -0.277 (± 0.216) | -0.273 (± 0.245) |

**Statistical analyses**

No statistical analyses for this end point

---

**Primary: Change in AUC for C-peptide from baseline to month 30**

---

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Change in AUC for C-peptide from baseline to month 30 <sup>[3]</sup> |
|-----------------|----------------------------------------------------------------------|

End point description:

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

End point timeframe:

Baseline to Month 30

Notes:

[3] - 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: The clinical study protocol defined statistical methods for efficacy data regarding C-peptide and immune system as well as Adverse events and other safety data as being composed of summary tables with descriptive statistics.

| End point values                     | Group A          | Group B          | Group C          | Group D          |
|--------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed          | 10               | 14               | 14               | 11               |
| Units: AUC for C-peptide (nmol/L)    |                  |                  |                  |                  |
| arithmetic mean (standard deviation) | -0.512 (± 0.318) | -0.383 (± 0.161) | -0.458 (± 0.209) | -0.405 (± 0.257) |

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Primary: Change in mean fasting C-peptide, baseline to month 6**

---

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Change in mean fasting C-peptide, baseline to month 6 <sup>[4]</sup> |
|-----------------|----------------------------------------------------------------------|

End point description:

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

End point timeframe:

Baseline to Visit 6

Notes:

[4] - 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: The clinical study protocol defined statistical methods for efficacy data regarding C-peptide and immune system as well as Adverse events and other safety data as being composed of summary tables with descriptive statistics.

| End point values                       | Group A          | Group B          | Group C          | Group D         |
|----------------------------------------|------------------|------------------|------------------|-----------------|
| Subject group type                     | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed            | 11               | 15               | 14               | 10              |
| Units: Mean fasting C-peptide (nmol/L) |                  |                  |                  |                 |
| arithmetic mean (standard deviation)   | -0.108 (± 0.195) | -0.015 (± 0.143) | -0.068 (± 0.133) | 0.023 (± 0.191) |

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in mean fasting C-peptide, baseline to month 15

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Change in mean fasting C-peptide, baseline to month 15 <sup>[5]</sup> |
|-----------------|-----------------------------------------------------------------------|

End point description:

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

End point timeframe:

Baseline to month 15

Notes:

[5] - 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: The clinical study protocol defined statistical methods for efficacy data regarding C-peptide and immune system as well as Adverse events and other safety data as being composed of summary tables with descriptive statistics.

| End point values                       | Group A          | Group B          | Group C          | Group D          |
|----------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type                     | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed            | 11               | 15               | 14               | 10               |
| Units: Mean fasting C-peptide (nmol/L) |                  |                  |                  |                  |
| arithmetic mean (standard deviation)   | -0.131 (± 0.166) | -0.061 (± 0.143) | -0.142 (± 0.133) | -0.039 (± 0.185) |

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in mean fasting C-peptide, baseline to month 30

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Change in mean fasting C-peptide, baseline to month 30 <sup>[6]</sup> |
|-----------------|-----------------------------------------------------------------------|

End point description:

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

End point timeframe:

Baseline to month 30

Notes:

[6] - 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: The clinical study protocol defined statistical methods for efficacy data regarding C-peptide and immune system as well as Adverse events and other safety data as being composed of summary tables with descriptive statistics.

| End point values                       | Group A          | Group B          | Group C          | Group D         |
|----------------------------------------|------------------|------------------|------------------|-----------------|
| Subject group type                     | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed            | 10               | 14               | 14               | 11              |
| Units: Mean fasting C-peptide (nmol/L) |                  |                  |                  |                 |
| arithmetic mean (standard deviation)   | -0.194 (± 0.204) | -0.134 (± 0.133) | -0.203 (± 0.124) | -0.13 (± 0.117) |

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in HbA1c from baseline to month 15

|                 |                                                          |
|-----------------|----------------------------------------------------------|
| End point title | Change in HbA1c from baseline to month 15 <sup>[7]</sup> |
|-----------------|----------------------------------------------------------|

End point description:

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

End point timeframe:

Baseline to 15 Months

Notes:

[7] - 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: The clinical study protocol defined statistical methods for efficacy data regarding C-peptide and immune system as well as Adverse events and other safety data as being composed of summary tables with descriptive statistics.

| End point values                     | Group A         | Group B          | Group C         | Group D         |
|--------------------------------------|-----------------|------------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group  | Reporting group | Reporting group |
| Number of subjects analysed          | 11              | 15               | 14              | 10              |
| Units: HbA1c (mmol/mol)              |                 |                  |                 |                 |
| arithmetic mean (standard deviation) | 5.455 (± 7.751) | 5.667 (± 15.407) | 5.643 (± 9.951) | 6.5 (± 10.967)  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in HbA1c from baseline to month 30

|                 |                                                          |
|-----------------|----------------------------------------------------------|
| End point title | Change in HbA1c from baseline to month 30 <sup>[8]</sup> |
|-----------------|----------------------------------------------------------|

End point description:

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

End point timeframe:

Baseline to Month 30.

Notes:

[8] - 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: The clinical study protocol defined statistical methods for efficacy data regarding C-peptide and immune system as well as Adverse events and other safety data as being composed of summary tables with descriptive statistics.

| <b>End point values</b>              | Group A             | Group B                | Group C               | Group D                |
|--------------------------------------|---------------------|------------------------|-----------------------|------------------------|
| Subject group type                   | Reporting group     | Reporting group        | Reporting group       | Reporting group        |
| Number of subjects analysed          | 10                  | 14                     | 14                    | 11                     |
| Units: HbA1c (mmol/mol)              |                     |                        |                       |                        |
| arithmetic mean (standard deviation) | 12.4 ( $\pm$ 5.816) | 13.286 ( $\pm$ 15.563) | 7.286 ( $\pm$ 11.323) | 10.909 ( $\pm$ 16.837) |

## Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events were recorded by the physician at every visit throughout the study.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Group A |
|-----------------------|---------|

Reporting group description:

Patients will be assigned to receive Ibuprofen as oral suspension; 400 mg every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd).

|                       |         |
|-----------------------|---------|
| Reporting group title | Group B |
|-----------------------|---------|

Reporting group description:

Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 1 subcutaneous injection with 20 µg Diamyd and one with placebo given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster dose (providing a total dose of 40 µg Diamyd).

|                       |         |
|-----------------------|---------|
| Reporting group title | Group C |
|-----------------------|---------|

Reporting group description:

Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and from Day 1 through 450 also oral drops of Vitamin D 2000 IU per day (i.e. 25 drops per day). In addition 2 subcutaneous injections with 20 µg Diamyd given at two different sites in the stomach area, each on Days 15 and 45, i.e., prime and booster doses (providing a total dose of 80µg Diamyd).

|                       |         |
|-----------------------|---------|
| Reporting group title | Group D |
|-----------------------|---------|

Reporting group description:

Patients will be assigned to receive placebo as oral suspension every morning from Day 1 through 90 and placebo oral drops from Day 1 through 450, and 2 subcutaneous injections with placebo (given at two different sites in the stomach area), each on Days 15 and 45

| Serious adverse events                            | Group A        | Group B         | Group C         |
|---------------------------------------------------|----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events |                |                 |                 |
| subjects affected / exposed                       | 0 / 16 (0.00%) | 3 / 16 (18.75%) | 2 / 16 (12.50%) |
| number of deaths (all causes)                     | 0              | 0               | 0               |
| number of deaths resulting from adverse events    | 0              | 0               | 0               |
| Injury, poisoning and procedural complications    |                |                 |                 |
| Upper limb fracture                               |                |                 |                 |
| subjects affected / exposed                       | 0 / 16 (0.00%) | 0 / 16 (0.00%)  | 0 / 16 (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           |
| Gastrointestinal disorders                        |                |                 |                 |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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          |
| Infections and infestations                     |                |                |                |
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (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          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Hypoglycaemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperglycaemia                                  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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>                     | Group D         |  |  |
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 2 / 15 (13.33%) |  |  |
| number of deaths (all causes)                     | 0               |  |  |
| number of deaths resulting from adverse events    | 0               |  |  |
| Injury, poisoning and procedural complications    |                 |  |  |
| Upper limb fracture                               |                 |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 15 (6.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Depression                                      |                |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Appendicitis                                    |                |  |  |
| subjects affected / exposed                     | 1 / 15 (6.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis                                 |                |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Hypoglycaemia                                   |                |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyperglycaemia                                  |                |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | Group A          | Group B          | Group C           |
|-------------------------------------------------------|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events |                  |                  |                   |
| subjects affected / exposed                           | 12 / 16 (75.00%) | 15 / 16 (93.75%) | 16 / 16 (100.00%) |
| Surgical and medical procedures                       |                  |                  |                   |
| Breast operation                                      |                  |                  |                   |
| subjects affected / exposed                           | 0 / 16 (0.00%)   | 1 / 16 (6.25%)   | 0 / 16 (0.00%)    |
| occurrences (all)                                     | 0                | 1                | 0                 |
| General disorders and administration site conditions  |                  |                  |                   |
| Injection site oedema                                 |                  |                  |                   |
| subjects affected / exposed                           | 0 / 16 (0.00%)   | 1 / 16 (6.25%)   | 1 / 16 (6.25%)    |
| occurrences (all)                                     | 0                | 2                | 1                 |
| Injection site rash                                   |                  |                  |                   |
| subjects affected / exposed                           | 1 / 16 (6.25%)   | 1 / 16 (6.25%)   | 0 / 16 (0.00%)    |
| occurrences (all)                                     | 1                | 2                | 0                 |
| Injection site reaction                               |                  |                  |                   |
| subjects affected / exposed                           | 5 / 16 (31.25%)  | 4 / 16 (25.00%)  | 6 / 16 (37.50%)   |
| occurrences (all)                                     | 8                | 5                | 7                 |
| Pyrexia                                               |                  |                  |                   |
| subjects affected / exposed                           | 0 / 16 (0.00%)   | 0 / 16 (0.00%)   | 2 / 16 (12.50%)   |
| occurrences (all)                                     | 0                | 0                | 2                 |
| Injection site pain                                   |                  |                  |                   |
| subjects affected / exposed                           | 0 / 16 (0.00%)   | 2 / 16 (12.50%)  | 1 / 16 (6.25%)    |
| occurrences (all)                                     | 0                | 3                | 1                 |
| Injection site nodule                                 |                  |                  |                   |
| subjects affected / exposed                           | 2 / 16 (12.50%)  | 1 / 16 (6.25%)   | 2 / 16 (12.50%)   |
| occurrences (all)                                     | 2                | 1                | 2                 |
| Injection site erythema                               |                  |                  |                   |
| subjects affected / exposed                           | 1 / 16 (6.25%)   | 1 / 16 (6.25%)   | 3 / 16 (18.75%)   |
| occurrences (all)                                     | 1                | 1                | 3                 |
| Injection site swelling                               |                  |                  |                   |
| subjects affected / exposed                           | 0 / 16 (0.00%)   | 0 / 16 (0.00%)   | 1 / 16 (6.25%)    |
| occurrences (all)                                     | 0                | 0                | 2                 |
| Injection site haematoma                              |                  |                  |                   |
| subjects affected / exposed                           | 0 / 16 (0.00%)   | 0 / 16 (0.00%)   | 1 / 16 (6.25%)    |
| occurrences (all)                                     | 0                | 0                | 1                 |
| Peripheral swelling                                   |                  |                  |                   |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Fatigue                                         |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                               | 0              | 0              | 2              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Epistaxis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Oropharyngeal pain                              |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                               | 1              | 0              | 1              |
| Psychiatric disorders                           |                |                |                |
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Obsessive-compulsive disorder                   |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Attention deficit/hyperactivity disorder        |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Investigations                                  |                |                |                |
| Blood cholesterol increased                     |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Haemoglobin decreased                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Injury, poisoning and procedural complications  |                |                |                |
| Back injury                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Road traffic accident                           |                |                |                |

|                                                                                                     |                     |                     |                     |
|-----------------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                                    | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                            | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)               | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)           | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Juvenile myoclonic epilepsy<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)            | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Abdominal pain                                                                                      |                     |                     |                     |

|                                        |                |                |                |
|----------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed            | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0              | 2              | 0              |
| Abdominal pain upper                   |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Gastritis                              |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Diarrhoea                              |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Coeliac disease                        |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Toothache                              |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Vomiting                               |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Skin and subcutaneous tissue disorders |                |                |                |
| Urticaria                              |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Pruritus genital                       |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Rash papular                           |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Eczema                                 |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Rash                                   |                |                |                |
| subjects affected / exposed            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |

|                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                      |                                                                                                       |                                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Acne<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                       | 0 / 16 (0.00%)<br>0                                                                                  | 0 / 16 (0.00%)<br>0                                                                                   | 0 / 16 (0.00%)<br>0                                                                                  |
| Renal and urinary disorders<br>Microalbuminuria<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                            | 0 / 16 (0.00%)<br>0                                                                                  | 0 / 16 (0.00%)<br>0                                                                                   | 1 / 16 (6.25%)<br>1                                                                                  |
| Endocrine disorders<br>Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                           | 0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0                                                       | 0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0                                                        | 1 / 16 (6.25%)<br>1<br><br>0 / 16 (0.00%)<br>0                                                       |
| Musculoskeletal and connective tissue disorders<br>Muscle twitching<br>subjects affected / exposed<br>occurrences (all)<br><br>Costochondritis<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                             | 0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0                                                       | 0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0                                                        | 1 / 16 (6.25%)<br>1<br><br>0 / 16 (0.00%)<br>0                                                       |
| Infections and infestations<br>Viral infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Ear infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Pharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection | 1 / 16 (6.25%)<br>1<br><br>1 / 16 (6.25%)<br>2<br><br>1 / 16 (6.25%)<br>1<br><br>0 / 16 (0.00%)<br>0 | 2 / 16 (12.50%)<br>2<br><br>0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0<br><br>1 / 16 (6.25%)<br>3 | 1 / 16 (6.25%)<br>1<br><br>0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0 |

|                                         |                 |                 |                 |
|-----------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed             | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 0               | 1               | 0               |
| Nasopharyngitis                         |                 |                 |                 |
| subjects affected / exposed             | 6 / 16 (37.50%) | 7 / 16 (43.75%) | 7 / 16 (43.75%) |
| occurrences (all)                       | 10              | 8               | 8               |
| Tonsillitis                             |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  |
| occurrences (all)                       | 0               | 1               | 1               |
| Viral upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                       | 0               | 0               | 1               |
| Pseudocroup                             |                 |                 |                 |
| subjects affected / exposed             | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 1               | 0               | 0               |
| Gastroenteritis                         |                 |                 |                 |
| subjects affected / exposed             | 1 / 16 (6.25%)  | 2 / 16 (12.50%) | 1 / 16 (6.25%)  |
| occurrences (all)                       | 1               | 3               | 1               |
| Tinea infection                         |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 0               | 0               | 0               |
| Influenza                               |                 |                 |                 |
| subjects affected / exposed             | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 1               | 0               | 0               |
| Cystitis                                |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 0               | 1               | 0               |
| Conjunctivitis                          |                 |                 |                 |
| subjects affected / exposed             | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 1               | 0               | 0               |
| Varicella                               |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                       | 0               | 0               | 1               |
| Rhinitis                                |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 2 / 16 (12.50%) |
| occurrences (all)                       | 0               | 0               | 2               |
| Borrelia infection                      |                 |                 |                 |

|                                    |                |                |                |
|------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed        | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                  | 1              | 0              | 0              |
| Infectious mononucleosis           |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                  | 0              | 0              | 1              |
| Metabolism and nutrition disorders |                |                |                |
| Hypoglycaemia                      |                |                |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                  | 0              | 0              | 1              |

|                                                       |                  |  |  |
|-------------------------------------------------------|------------------|--|--|
| <b>Non-serious adverse events</b>                     | Group D          |  |  |
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 14 / 15 (93.33%) |  |  |
| Surgical and medical procedures                       |                  |  |  |
| Breast operation                                      |                  |  |  |
| subjects affected / exposed                           | 0 / 15 (0.00%)   |  |  |
| occurrences (all)                                     | 0                |  |  |
| General disorders and administration site conditions  |                  |  |  |
| Injection site oedema                                 |                  |  |  |
| subjects affected / exposed                           | 1 / 15 (6.67%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Injection site rash                                   |                  |  |  |
| subjects affected / exposed                           | 0 / 15 (0.00%)   |  |  |
| occurrences (all)                                     | 0                |  |  |
| Injection site reaction                               |                  |  |  |
| subjects affected / exposed                           | 6 / 15 (40.00%)  |  |  |
| occurrences (all)                                     | 7                |  |  |
| Pyrexia                                               |                  |  |  |
| subjects affected / exposed                           | 2 / 15 (13.33%)  |  |  |
| occurrences (all)                                     | 2                |  |  |
| Injection site pain                                   |                  |  |  |
| subjects affected / exposed                           | 0 / 15 (0.00%)   |  |  |
| occurrences (all)                                     | 0                |  |  |
| Injection site nodule                                 |                  |  |  |
| subjects affected / exposed                           | 2 / 15 (13.33%)  |  |  |
| occurrences (all)                                     | 3                |  |  |
| Injection site erythema                               |                  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Injection site swelling                         |                 |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Injection site haematoma                        |                 |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Peripheral swelling                             |                 |  |  |
| subjects affected / exposed                     | 1 / 15 (6.67%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Fatigue                                         |                 |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Epistaxis                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 15 (13.33%) |  |  |
| occurrences (all)                               | 2               |  |  |
| Oropharyngeal pain                              |                 |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Psychiatric disorders                           |                 |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 15 (6.67%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Obsessive-compulsive disorder                   |                 |  |  |
| subjects affected / exposed                     | 1 / 15 (6.67%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Attention deficit/hyperactivity disorder        |                 |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Investigations                                  |                 |  |  |
| Blood cholesterol increased                     |                 |  |  |
| subjects affected / exposed                     | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Haemoglobin decreased                           |                 |  |  |

|                                                  |                     |  |  |
|--------------------------------------------------|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 |  |  |
| Injury, poisoning and procedural complications   |                     |  |  |
| Back injury                                      |                     |  |  |
| subjects affected / exposed                      | 0 / 15 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Road traffic accident                            |                     |  |  |
| subjects affected / exposed                      | 1 / 15 (6.67%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Fall                                             |                     |  |  |
| subjects affected / exposed                      | 0 / 15 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Dermatitis contact                               |                     |  |  |
| subjects affected / exposed                      | 1 / 15 (6.67%)      |  |  |
| occurrences (all)                                | 2                   |  |  |
| Ligament sprain                                  |                     |  |  |
| subjects affected / exposed                      | 1 / 15 (6.67%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Cardiac disorders                                |                     |  |  |
| Palpitations                                     |                     |  |  |
| subjects affected / exposed                      | 0 / 15 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Tachycardia                                      |                     |  |  |
| subjects affected / exposed                      | 0 / 15 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Nervous system disorders                         |                     |  |  |
| Dizziness                                        |                     |  |  |
| subjects affected / exposed                      | 0 / 15 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Headache                                         |                     |  |  |
| subjects affected / exposed                      | 1 / 15 (6.67%)      |  |  |
| occurrences (all)                                | 2                   |  |  |
| Juvenile myoclonic epilepsy                      |                     |  |  |
| subjects affected / exposed                      | 0 / 15 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Blood and lymphatic system disorders             |                     |  |  |

|                                                                          |                      |  |  |
|--------------------------------------------------------------------------|----------------------|--|--|
| Anaemia<br>subjects affected / exposed<br>occurrences (all)              | 1 / 15 (6.67%)<br>1  |  |  |
| Gastrointestinal disorders                                               |                      |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 1 / 15 (6.67%)<br>1  |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 2 / 15 (13.33%)<br>2 |  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0  |  |  |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)            | 2 / 15 (13.33%)<br>2 |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 2 / 15 (13.33%)<br>2 |  |  |
| Coeliac disease<br>subjects affected / exposed<br>occurrences (all)      | 0 / 15 (0.00%)<br>0  |  |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)            | 1 / 15 (6.67%)<br>1  |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 0 / 15 (0.00%)<br>0  |  |  |
| Skin and subcutaneous tissue disorders                                   |                      |  |  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)            | 1 / 15 (6.67%)<br>1  |  |  |
| Pruritus genital<br>subjects affected / exposed<br>occurrences (all)     | 1 / 15 (6.67%)<br>1  |  |  |
| Rash papular                                                             |                      |  |  |

|                                                                                                                                                                                                                                                                                       |                                                                                                                             |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Eczema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Acne</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 15 (6.67%)</p> <p>1</p> <p>0 / 15 (0.00%)</p> <p>0</p> <p>1 / 15 (6.67%)</p> <p>1</p> <p>1 / 15 (6.67%)</p> <p>1</p> |  |  |
| <p>Renal and urinary disorders</p> <p>Microalbuminuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                                                | <p>0 / 15 (0.00%)</p> <p>0</p>                                                                                              |  |  |
| <p>Endocrine disorders</p> <p>Hyperthyroidism</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypothyroidism</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                       | <p>0 / 15 (0.00%)</p> <p>0</p> <p>1 / 15 (6.67%)</p> <p>1</p>                                                               |  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Muscle twitching</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Costochondritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                         | <p>0 / 15 (0.00%)</p> <p>0</p> <p>1 / 15 (6.67%)</p> <p>1</p>                                                               |  |  |
| <p>Infections and infestations</p> <p>Viral infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ear infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                | <p>0 / 15 (0.00%)</p> <p>0</p> <p>0 / 15 (0.00%)</p> <p>0</p>                                                               |  |  |

|                                         |                 |  |  |
|-----------------------------------------|-----------------|--|--|
| Pharyngitis                             |                 |  |  |
| subjects affected / exposed             | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                       | 0               |  |  |
| Upper respiratory tract infection       |                 |  |  |
| subjects affected / exposed             | 3 / 15 (20.00%) |  |  |
| occurrences (all)                       | 4               |  |  |
| Urinary tract infection                 |                 |  |  |
| subjects affected / exposed             | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                       | 0               |  |  |
| Nasopharyngitis                         |                 |  |  |
| subjects affected / exposed             | 4 / 15 (26.67%) |  |  |
| occurrences (all)                       | 4               |  |  |
| Tonsillitis                             |                 |  |  |
| subjects affected / exposed             | 1 / 15 (6.67%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Viral upper respiratory tract infection |                 |  |  |
| subjects affected / exposed             | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                       | 0               |  |  |
| Pseudocroup                             |                 |  |  |
| subjects affected / exposed             | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                       | 0               |  |  |
| Gastroenteritis                         |                 |  |  |
| subjects affected / exposed             | 1 / 15 (6.67%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Tinea infection                         |                 |  |  |
| subjects affected / exposed             | 1 / 15 (6.67%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Influenza                               |                 |  |  |
| subjects affected / exposed             | 3 / 15 (20.00%) |  |  |
| occurrences (all)                       | 3               |  |  |
| Cystitis                                |                 |  |  |
| subjects affected / exposed             | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                       | 0               |  |  |
| Conjunctivitis                          |                 |  |  |
| subjects affected / exposed             | 0 / 15 (0.00%)  |  |  |
| occurrences (all)                       | 0               |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| Varicella                          |                |  |  |
| subjects affected / exposed        | 0 / 15 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Rhinitis                           |                |  |  |
| subjects affected / exposed        | 0 / 15 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Borrelia infection                 |                |  |  |
| subjects affected / exposed        | 0 / 15 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Infectious mononucleosis           |                |  |  |
| subjects affected / exposed        | 0 / 15 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Metabolism and nutrition disorders |                |  |  |
| Hypoglycaemia                      |                |  |  |
| subjects affected / exposed        | 0 / 15 (0.00%) |  |  |
| occurrences (all)                  | 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**

None reported