



## Clinical trial results:

### Effects of perioperative administration of dexamethasone on postoperative complications and mortality after non-cardiac major surgery : a randomized, multicentre, double blind, study

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2017-000442-21 |
| Trial protocol           | FR             |
| Global end of trial date | 16 April 2019  |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)                                     |
| This version publication date     | 20 April 2022                                    |
| First version publication date    | 20 April 2022                                    |
| Summary attachment (see zip file) | Summary (MEDICAMENT Résumé du rapport final.pdf) |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | RC17_0029 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03218553 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | CHU de Nantes   |
| Sponsor organisation address | 5,Allée de l'île Gloriette, Nantes, France,                             |
| Public contact               | June FORTIN, CHU de Nantes, 0033 253482844, bp-prom-reglu@chu-nantes.fr |
| Scientific contact           | June FORTIN, CHU de Nantes, 0033 253482844, bp-prom-regl@chu-nantes.fr  |

Notes:

##### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 05 November 2020 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 16 April 2019    |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 16 April 2019    |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

Evaluate the effectiveness of perioperative administration of corticosteroid to reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery

Protection of trial subjects:

Patients were informed in complete and faithful terms and in understandable language of the objectives and constraints of the study, the potential risks, the required observation and safety measures, and their right to refuse to participate in the study or to revoke their consent at any time.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 06 November 2017 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | France: 1222 |
| Worldwide total number of subjects   | 1222         |
| EEA total number of subjects         | 1222         |

Notes:

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**Subjects enrolled per age group**

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 289 |
| From 65 to 84 years                       | 885 |
| 85 years and over                         | 48  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All consecutive adult patients requiring major surgery with an expected duration  $\geq 90$  minutes, provided they satisfied at least 1 of the high-risk criteria will be assessed for eligibility.

### Period 1

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

Blinding implementation details:

All members of the surgical unit, including the anesthesiologist and the surgeon, will remain blinded to the allocated treatment group.

### Arms

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

Arm description:

dexamethasone: first dose: 0,2mg.kg-1 at the end of the surgical procedure, second dose (0,2mg.kg-1) 24 hours after the surgery

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Experimental                        |
| Investigational medicinal product name | DEXAMETHASONE                       |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Solution for solution for injection |
| Routes of administration               | Intravenous use                     |

Dosage and administration details:

DESAMETHASONE MYLAN 20 mg/ml

2 times in 24 Hours : the first one at the end of surgery and the second one 24 Hours after the surgery

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Control group : placebo |
|------------------|-------------------------|

Arm description:

administration of a first dose of placebo dexamethasone given intravenously just after surgery. A second dose (0.2 mg.kg-1) is given intravenously at day +1

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Placebo                             |
| Investigational medicinal product name | CHLORURE DE SODIUM                  |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Solution for solution for injection |
| Routes of administration               | Intravenous use                     |

Dosage and administration details:

CHLORURE DE SODIUM LAVOISIER 0.9 POUR CENT

2 times in 24 Hours : the first one at the end of surgery and the second one 24 Hours after the surgery

| <b>Number of subjects in period 1</b> | Experimental group | Control group :<br>placebo |
|---------------------------------------|--------------------|----------------------------|
| Started                               | 613                | 609                        |
| Completed                             | 601                | 593                        |
| Not completed                         | 12                 | 16                         |
| Surgery Cancelled                     | -                  | 3                          |
| Did not receive injection             | -                  | 4                          |
| UNKNOWN                               | 5                  | -                          |
| FORGET                                | 1                  | -                          |
| Protocol deviation                    | 6                  | 9                          |

## Baseline characteristics

### Reporting groups

|  |                         |
|--|-------------------------|
| Reporting group title  | Experimental group      |
| Reporting group description:<br>dexamethasone: first dose: 0,2mg.kg-1 at the<br>end of the surgical procedure, second dose (0,2mg.kg-1) 24 hours<br>after the surgery                              |                         |
| Reporting group title  | Control group : placebo |
| Reporting group description:<br>administration of a first dose of placebo dexamethasone given<br>intravenously just after surgery. A second dose (0.2 mg.kg-1) is given intravenously at<br>day +1 |                         |

| Reporting group values                                | Experimental group | Control group :<br>placebo | Total |
|---|--------------------|----------------------------|-------|
| Number of subjects                                    | 613                | 609                        | 1222  |
| Age categorical<br>Units: Subjects                    |                    |                            |       |
| In utero  | 0                  | 0                          | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                  | 0                          | 0     |
| Newborns (0-27 days)                                  | 0                  | 0                          | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0                  | 0                          | 0     |
| Children (2-11 years)                                 | 0                  | 0                          | 0     |
| Adolescents (12-17 years)                             | 0                  | 0                          | 0     |
| Adults (18-64 years)                                  | 155                | 134                        | 289   |
| From 65-84 years                                      | 435                | 450                        | 885   |
| 85 years and over                                     | 23                 | 25                         | 48    |
| Gender categorical<br>Units: Subjects                 |                    |                            |       |
| Female  | 223                | 227                        | 450   |
| Male  | 390                | 382                        | 772   |

### Subject analysis sets

|   |                             |
|---|-----------------------------|
| Subject analysis set title  | mITT                        |
| Subject analysis set type   | Modified intention-to-treat |
| Subject analysis set description:<br>The main analysis of the primary outcome was conducted in the modified intention-to-treat<br>population, defined as all randomised participants except those who would have no longer been<br>considered eligible for randomisation at the time of first treatment injection or who would never had any<br>injection of the study treatment. |                             |

| Reporting group values                                | mITT |  |  |
|---|------|--|--|
| Number of subjects                                    | 1184 |  |  |
| Age categorical<br>Units: Subjects                    |      |  |  |
| In utero  |      |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) |      |  |  |

|   |     |  |  |
|---|-----|--|--|
| Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |     |  |  |
| Gender categorical<br>Units: Subjects   |     |  |  |
| Female  | 436 |  |  |
| Male  | 748 |  |  |

## End points

### End points reporting groups

|   |                             |
|---|-----------------------------|
| Reporting group title   | Experimental group          |
| Reporting group description:<br>dexamethasone: first dose: 0,2mg.kg-1 at the<br>end of the surgical procedure, second dose (0,2mg.kg-1) 24 hours<br>after the surgery   |                             |
| Reporting group title   | Control group : placebo     |
| Reporting group description:<br>administration of a first dose of placebo dexamethasone given<br>intravenously just after surgery. A second dose (0.2 mg.kg-1) is given intravenously at<br>day +1  |                             |
| Subject analysis set title  | mITT                        |
| Subject analysis set type   | Modified intention-to-treat |
| Subject analysis set description:<br>The main analysis of the primary outcome was conducted in the modified intention-to-treat<br>population, defined as all randomised participants except those who would have no longer been<br>considered eligible for randomisation at the time of first treatment injection or who would never had any<br>injection of the study treatment. |                             |

### Primary: All cause mortality or major postoperative complications within 14 days after surgery

|   |  |
|---|--|
| End point title   | All cause mortality or major postoperative complications within<br>14 days after surgery |
| End point description:<br>The primary outcome was a composite of postoperative complications or all cause mortality within 14<br>days after surgery, assessed in the modified intention-to-treat population (at least one treatment<br>administered). |  |
| End point type  | Primary  |
| End point timeframe:<br>14 DAYS   |  |

| End point values            | Experimental<br>group | Control group :<br>placebo | mITT                 |  |
|-----------------------------|-----------------------|----------------------------|----------------------|--|
| Subject group type          | Reporting group       | Reporting group            | Subject analysis set |  |
| Number of subjects analysed | 595                   | 589                        | 1184                 |  |
| Units: number of subjects   |                       |                            |                      |  |
| number (not applicable)     | 101                   | 117                        | 218                  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Primary analysis                             |
| Statistical analysis description:<br>Data are analyzed with the use of logistic regression adjusted for stratification factors (cancer and type<br>of surgery). |  |
| Comparison groups   | Control group : placebo v Experimental group |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 1184                  |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| P-value                                 | < 0.05 <sup>[1]</sup> |
| Method                                  | Regression, Logistic  |

Notes:

[1] - All statistical analyzes will take into account stratified randomization (cancer and type of surgery) as recommended in the CONSORT 2010 statement and in the literature [Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. C



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

28 Days

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Experimental |
|-----------------------|--------------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events  | Experimental       | Placebo            |  |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                    |                    |  |
| subjects affected / exposed   | 110 / 601 (18.30%) | 108 / 593 (18.21%) |  |
| number of deaths (all causes)                                       | 10                 | 12                 |  |
| number of deaths resulting from adverse events                      |                    |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Neoplasms benign, malignant and unspecified                         |                    |                    |  |
| subjects affected / exposed   | 0 / 601 (0.00%)    | 1 / 593 (0.17%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 1              |  |
| Vascular disorders  |                    |                    |  |
| Vascular disorders  |                    |                    |  |
| subjects affected / exposed   | 14 / 601 (2.33%)   | 11 / 593 (1.85%)   |  |
| occurrences causally related to treatment / all                     | 1 / 14             | 2 / 12             |  |
| deaths causally related to treatment / all                          | 0 / 1              | 0 / 3              |  |
| General disorders and administration site conditions                |                    |                    |  |
| General disorders and administration site conditions                |                    |                    |  |
| subjects affected / exposed   | 9 / 601 (1.50%)    | 4 / 593 (0.67%)    |  |
| occurrences causally related to treatment / all                     | 2 / 10             | 0 / 4              |  |
| deaths causally related to treatment / all                          | 0 / 2              | 0 / 0              |  |
| Reproductive system and breast disorders                            |                    |                    |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Reproductive system and breast disorders        |                  |                  |  |
| subjects affected / exposed                     | 0 / 601 (0.00%)  | 1 / 593 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| subjects affected / exposed                     | 24 / 601 (3.99%) | 21 / 593 (3.54%) |  |
| occurrences causally related to treatment / all | 2 / 26           | 1 / 26           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| Psychiatric disorders                           |                  |                  |  |
| Psychiatric disorders                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 601 (0.00%)  | 2 / 593 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Product issues                                  |                  |                  |  |
| Product issues                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 601 (0.17%)  | 0 / 593 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| subjects affected / exposed                     | 19 / 601 (3.16%) | 27 / 593 (4.55%) |  |
| occurrences causally related to treatment / all | 2 / 22           | 3 / 28           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                  |                  |  |
| Congenital , familial and genetic disorders     |                  |                  |  |
| subjects affected / exposed                     | 0 / 601 (0.00%)  | 1 / 593 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac disorders                               |                  |                  |  |
| Cardiac disorder                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 7 / 601 (1.16%)  | 2 / 593 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1            |  |
| Nervous system disorders                        |                  |                  |  |
| Nervous system disorder                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 601 (0.67%)  | 0 / 593 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| subjects affected / exposed                     | 2 / 601 (0.33%)  | 1 / 593 (0.17%)  |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Gastrointestinal disorders                      |                  |                  |  |
| subjects affected / exposed                     | 19 / 601 (3.16%) | 21 / 593 (3.54%) |  |
| occurrences causally related to treatment / all | 4 / 22           | 1 / 27           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Hepatobiliary disorder                          |                  |                  |  |
| subjects affected / exposed                     | 3 / 601 (0.50%)  | 3 / 593 (0.51%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 2 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| subjects affected / exposed                     | 1 / 601 (0.17%)  | 2 / 593 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Renal and urinary disorders                     |                  |                  |  |
| subjects affected / exposed                     | 4 / 601 (0.67%)  | 7 / 593 (1.18%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| subjects affected / exposed                     | 2 / 601 (0.33%)  | 1 / 593 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Infections and Infestations                     |                  |                  |  |
| subjects affected / exposed                     | 37 / 601 (6.16%) | 31 / 593 (5.23%) |  |
| occurrences causally related to treatment / all | 13 / 42          | 9 / 34           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| subjects affected / exposed                     | 2 / 601 (0.33%)  | 5 / 593 (0.84%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                                   | Experimental       | Placebo            |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events               |                    |                    |  |
| subjects affected / exposed   | 202 / 601 (33.61%) | 212 / 593 (35.75%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| subjects affected / exposed   | 0 / 601 (0.00%)    | 1 / 593 (0.17%)    |  |
| occurrences (all)   | 0                  | 1                  |  |
| Vascular disorders  |                    |                    |  |
| Vascular disorders  |                    |                    |  |
| subjects affected / exposed   | 25 / 601 (4.16%)   | 17 / 593 (2.87%)   |  |
| occurrences (all)   | 25                 | 17                 |  |
| Surgical and medical procedures                                     |                    |                    |  |
| Surgical and medical procedures                                     |                    |                    |  |
| subjects affected / exposed   | 1 / 601 (0.17%)    | 1 / 593 (0.17%)    |  |
| occurrences (all)   | 1                  | 1                  |  |
| General disorders and administration site conditions                |                    |                    |  |
| General disorders and administration site conditions                |                    |                    |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 6 / 601 (1.00%)<br>6   | 14 / 593 (2.36%)<br>14 |  |
| Immune system disorders<br>Immune system disorders<br>subjects affected / exposed<br>occurrences (all)   | 3 / 601 (0.50%)<br>3   | 0 / 593 (0.00%)<br>0   |  |
| Reproductive system and breast disorders<br>Reproductive system and breast disorders<br>subjects affected / exposed<br>occurrences (all)               | 2 / 601 (0.33%)<br>2   | 1 / 593 (0.17%)<br>1   |  |
| Respiratory, thoracic and mediastinal disorders<br>Respiratory, thoracic and mediastinal disorders<br>subjects affected / exposed<br>occurrences (all) | 19 / 601 (3.16%)<br>19 | 19 / 593 (3.20%)<br>19 |  |
| Psychiatric disorders<br>Psychiatric disorders<br>subjects affected / exposed<br>occurrences (all)   | 8 / 601 (1.33%)<br>8   | 5 / 593 (0.84%)<br>5   |  |
| Investigations<br>Investigations<br>subjects affected / exposed<br>occurrences (all)   | 2 / 601 (0.33%)<br>2   | 5 / 593 (0.84%)<br>5   |  |
| Injury, poisoning and procedural complications<br>Injury, poisoning and procedural complications<br>subjects affected / exposed<br>occurrences (all)   | 20 / 601 (3.33%)<br>20 | 24 / 593 (4.05%)<br>24 |  |
| Cardiac disorders<br>Cardiac disorders<br>subjects affected / exposed<br>occurrences (all)   | 3 / 601 (0.50%)<br>3   | 6 / 593 (1.01%)<br>6   |  |
| Nervous system disorders<br>Nervous system disorders<br>subjects affected / exposed<br>occurrences (all)   | 2 / 601 (0.33%)<br>2   | 3 / 593 (0.51%)<br>3   |  |
| Blood and lymphatic system disorders   |                        |                        |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| Blood and lymphatic system disorders<br>subjects affected / exposed<br>occurrences (all)   | 7 / 601 (1.16%)<br>7   | 7 / 593 (1.18%)<br>7   |  |
| Eye disorders<br>Eye disorders<br>subjects affected / exposed<br>occurrences (all)   | 1 / 601 (0.17%)<br>1   | 0 / 593 (0.00%)<br>0   |  |
| Gastrointestinal disorders<br>Gastrointestinal disorders<br>subjects affected / exposed<br>occurrences (all)   | 31 / 601 (5.16%)<br>31 | 36 / 593 (6.07%)<br>36 |  |
| Hepatobiliary disorders<br>Hepatobiliary disorders<br>subjects affected / exposed<br>occurrences (all)   | 8 / 601 (1.33%)<br>8   | 5 / 593 (0.84%)<br>5   |  |
| Skin and subcutaneous tissue disorders<br>Skin and subcutaneous tissue disorders<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 601 (0.33%)<br>2   | 0 / 593 (0.00%)<br>0   |  |
| Renal and urinary disorders<br>Renal and urinary disorders<br>subjects affected / exposed<br>occurrences (all)   | 8 / 601 (1.33%)<br>8   | 16 / 593 (2.70%)<br>16 |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal and connective tissue disorders<br>subjects affected / exposed<br>occurrences (all) | 7 / 601 (1.16%)<br>7   | 5 / 593 (0.84%)<br>5   |  |
| Infections and infestations<br>Infections and infestations<br>subjects affected / exposed<br>occurrences (all)   | 42 / 601 (6.99%)<br>42 | 38 / 593 (6.41%)<br>38 |  |
| Metabolism and nutrition disorders<br>Metabolism and nutrition disorders<br>subjects affected / exposed<br>occurrences (all)                           | 14 / 601 (2.33%)<br>14 | 15 / 593 (2.53%)<br>15 |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment   |
|-------------|---|
| 04 May 2018 | Modification of the list of investigators with the deletion of investigator centres<br>Modification of principal investigators and the addition of centers<br>Modification of the pharmacovigilance part of the protocol with clarifications on the notification of SAEs.<br>Clarifications of the statistical part<br>Modification of the DSMB following the death of one of the members<br>Details on the inclusion and non-inclusion criteria and the maximum dosage of dexamethasone used |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34078591>