



## Clinical trial results:

### An open label pragmatic randomised controlled trial of nicotine patch preloading for smoking cessation.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-005134-19 |
| Trial protocol           | GB             |
| Global end of trial date | 12 May 2016    |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 28 April 2017 |
| First version publication date | 28 April 2017 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | RG_11-171 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN33031001 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University of Oxford   |
| Sponsor organisation address | Churchill Hospital, Oxford, United Kingdom, OX3 7LE                                  |
| Public contact               | Heather House, University of Oxford, 0044 01865 572245, heather.house@admin.ox.ac.uk |
| Scientific contact           | Heather House, University of Oxford, 0044 01865 572245, heather.house@admin.ox.ac.uk |

Notes:

#### Paediatric regulatory details

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

Notes:

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## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 01 January 2017 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 12 May 2016     |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 12 May 2016     |
| Was the trial ended prematurely?                     | No              |

Notes:

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## General information about the trial

Main objective of the trial:

The objectives are:

1. To examine the relative efficacy of nicotine patch worn for four weeks prior to quitting plus standard NHS care post-quit versus standard care only in smokers undergoing NHS treatment for tobacco dependence.
2. To examine the adverse effects and safety of the nicotine pre-treatment.

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Protection of trial subjects:

A risk assessment was carried out in accordance with MHRA guidance on Risk Adapted Approaches to Monitoring. A suitable monitoring plan was drawn up and appropriate on-site and central monitoring performed.

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Background therapy:

In both arms, at the first and second contacts in both arms, we facilitated contact between the participant and the local stop smoking services and wrote a referral letter to encourage the stop smoking service to work with us on respecting the preloading treatment. In particular, we asked the stop smoking advisors to ignore the presence or absence of preloading when discussing and recommending pharmacotherapy for use to support the quit attempt. We especially asked advisors to feel free to use varenicline, which starts prior to quit day and hence would be used concurrently with nicotine preloading. This is because we were keen that the treatment provided by the stop smoking services did not differ between trial arms.

The NHS trains stop smoking advisors to give weekly behavioural support starting 1-2 weeks prior to quit day and continuing until at least four weeks after quit day. This support addresses issues such as planning for the quit day, the 'not a puff rule', and how to deal with difficult situations, such as others smoking around the quitter. It also provides monitoring of behaviour and validation of abstinence through carbon monoxide testing. The support is largely withdrawal-orientated therapy.

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Evidence for comparator:

The research team were keen to offer participants in the control arm a placebo, but the funding would not allow this. We were concerned that offering no treatment would lead to disengagement and, to counteract this, we developed a behavioural intervention which could seem plausible to participants but had no evidence that it would increase abstinence. We asked participants to consider their smoking pattern, the triggers for particular cigarettes, and to plan ways to reduce these cues. Such a process is standard in smoking cessation support anyway, so that participants in the intervention group were likely to engage in this after preloading and in preparation for quitting. As in the intervention group, the control group received a booklet outlining this process, which was designed to be comparable to the booklet supplied to the intervention group. As in the intervention group, participants in the control group were referred to the NHS Stop Smoking Service to commence a quit attempt between three and five weeks after enrolment.

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 13 August 2012 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

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|                                      |                      |
|--------------------------------------|----------------------|
| Country: Number of subjects enrolled | United Kingdom: 1792 |
| Worldwide total number of subjects   | 1792                 |
| EEA total number of subjects         | 1792                 |

Notes:

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#### Subjects enrolled per age group

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|   |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 1561 |
| From 65 to 84 years                       | 229  |
| 85 years and over                         | 2    |

## Subject disposition

### Recruitment

Recruitment details:

four recruitment centres Birmingham, Bristol and Nottingham, all recruiting between 1 February 2012 and March 2016

### Pre-assignment

Screening details:

Inclusion criteria:

Regular smokers of cigarettes, cigars, and rollup tobacco cigarettes, with or without marijuana aged  $\geq 18$  years of age.

People who would be suitable for preloading in the judgement of the researcher

Prepared to set a quit day in four weeks.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

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

Arm description:

In the intervention arm, participants wore a 21mg nicotine patch daily for an intended four weeks prior to quit day.

|  |                                    |
|--|------------------------------------|
| Arm type                               | Experimental                       |
| Investigational medicinal product name | Nicotine replacement therapy patch |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Transdermal patch                  |
| Routes of administration               | Transdermal use                    |

Dosage and administration details:

21 mg Niquitin CQ Glaxo Smith Kline Consumer Healthcare daily nicotine patch worn for four weeks before their smoking quit day, from the day of their enrolment. They were advised to wear the patch for 24 hours a day.

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

Arm description:

standard smoking cessation support only

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

| Number of subjects in period 1 | preloading | control |
|--------------------------------|------------|---------|
| Started                        | 899        | 893     |
| 6 months                       | 728        | 733     |
| Completed                      | 689        | 700     |
| Not completed                  | 210        | 193     |
| Adverse event, serious fatal   | -          | 2       |

|                   |     |     |
|-------------------|-----|-----|
| died              | 4   | -   |
| Lost to follow-up | 195 | 171 |
| withdrawn         | 11  | 20  |

## Baseline characteristics

### Reporting groups

|  |            |
|--|------------|
| Reporting group title  | preloading |
| Reporting group description:<br>In the intervention arm, participants wore a 21mg nicotine patch daily for an intended four weeks prior to quit day. |            |
| Reporting group title  | control    |
| Reporting group description:<br>standard smoking cessation support only  |            |

| Reporting group values                             | preloading | control | Total |
|--|------------|---------|-------|
| Number of subjects                                 | 899        | 893     | 1792  |
| Age categorical                                    |            |         |       |
| Units: Subjects                                    |            |         |       |
| In utero   |            |         | 0     |
| Preterm newborn infants (gestational age < 37 wks) |            |         | 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)                               |            |         | 0     |
| From 65-84 years                                   |            |         | 0     |
| 85 years and over                                  |            |         | 0     |
| Age continuous                                     |            |         |       |
| age continuous                                     |            |         |       |
| Units: years                                       |            |         |       |
| arithmetic mean                                    | 49.1       | 48.8    |       |
| standard deviation                                 | ± 13.3     | ± 13.4  | -     |
| Gender categorical                                 |            |         |       |
| Units: Subjects                                    |            |         |       |
| Female   | 426        | 423     | 849   |
| Male   | 473        | 470     | 943   |
| carbon monoxide                                    |            |         |       |
| carbon monoxide reading                            |            |         |       |
| Units: parts per million                           |            |         |       |
| arithmetic mean                                    | 23.5       | 23.8    |       |
| standard deviation                                 | ± 12.3     | ± 12.8  | -     |
| nicotine dependence                                |            |         |       |
| nicotine dependence (NCSCT)                        |            |         |       |
| Units: scale 0 to 10                               |            |         |       |
| arithmetic mean                                    | 5.22       | 5.2     |       |
| standard deviation                                 | ± 2.2      | ± 2.24  | -     |

### Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT                |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

all patients randomised irrespective of whether the participants received any trial medication and irrespective of whether they completed

|   |        |  |  |
|---|--------|--|--|
| <b>Reporting group values</b>   | ITT    |  |  |
| Number of subjects  | 1792   |  |  |
| Age categorical   |        |  |  |
| Units: Subjects   |        |  |  |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23<br>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 |        |  |  |
| Age continuous  |        |  |  |
| age continuous  |        |  |  |
| Units: years  |        |  |  |
| arithmetic mean   | 48.9   |  |  |
| standard deviation  | ± 13.4 |  |  |
| Gender categorical  |        |  |  |
| Units: Subjects   |        |  |  |
| Female  | 849    |  |  |
| Male  | 943    |  |  |
| carbon monoxide   |        |  |  |
| carbon monoxide reading   |        |  |  |
| Units: parts per million  |        |  |  |
| arithmetic mean   | 23.7   |  |  |
| standard deviation  | ± 12.5 |  |  |
| nicotine dependence   |        |  |  |
| nicotine dependence (NCSCT)   |        |  |  |
| Units: scale 0 to 10  |        |  |  |
| arithmetic mean   | 5.21   |  |  |
| standard deviation  | ± 2.2  |  |  |

## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | preloading         |
| Reporting group description:<br>In the intervention arm, participants wore a 21mg nicotine patch daily for an intended four weeks prior to quit day.                           |                    |
| Reporting group title  | control            |
| Reporting group description:<br>standard smoking cessation support only  |                    |
| Subject analysis set title   | ITT                |
| Subject analysis set type  | Intention-to-treat |
| Subject analysis set description:<br>all patients randomised irrespective of whether the participants received any trial medication and irrespective of whether they completed |                    |

### Primary: smoking abstinence at 6 months (russell criteria)

|   |   |
|---|---|
| End point title   | smoking abstinence at 6 months (russell criteria) |
| End point description:<br>smoking abstinence 6 months after quit date |   |
| End point type  | Primary   |
| End point timeframe:<br>6 months after quit date                      |   |

| End point values            | preloading         | control            |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 899 <sup>[1]</sup> | 893 <sup>[2]</sup> |  |  |
| Units: 0 1                  |                    |                    |  |  |
| no                          | 573                | 608                |  |  |
| yes                         | 326                | 285                |  |  |

Notes:

[1] - ITT

[2] - ITT

### Statistical analyses

|   |                        |
|---|------------------------|
| Statistical analysis title  | abstinence at 6 months |
| Statistical analysis description:<br>logistic regression with adjustment for centre |                        |
| Comparison groups   | preloading v control   |
| Number of subjects included in analysis   | 1792                   |
| Analysis specification  | Pre-specified          |
| Analysis type   | superiority            |
| P-value   | = 0.081                |
| Method  | Regression, Logistic   |
| Parameter estimate  | Odds ratio (OR)        |
| Point estimate  | 1.25                   |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.97    |
| upper limit         | 1.62    |

### Secondary: russell standard abstinence at 4 weeks

|   |  |
|---|--|
| End point title   | russell standard abstinence at 4 weeks |
| End point description:<br>validated abstinence at 4 weeks after quit date |  |
| End point type  | Secondary                              |
| End point timeframe:<br>4 weeks after quit date                           |  |

| End point values            | preloading      | control         | ITT                  |  |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed | 899             | 893             | 1792                 |  |
| Units: 0 1                  |                 |                 |                      |  |
| no                          | 573             | 608             | 1181                 |  |
| yes                         | 326             | 285             | 611                  |  |

### Statistical analyses

|  |                                 |
|--|---------------------------------|
| Statistical analysis title   | validated abstinence at 4 weeks |
| Statistical analysis description:<br>logistic regression for validated abstinence at 4 weeks adjusted for centre |                                 |
| Comparison groups  | preloading v control            |
| Number of subjects included in analysis  | 1792                            |
| Analysis specification   | Pre-specified                   |
| Analysis type  | superiority                     |
| P-value  | = 0.053                         |
| Method   | Regression, Logistic            |
| Parameter estimate   | Odds ratio (OR)                 |
| Point estimate   | 1.21                            |
| Confidence interval  |                                 |
| level  | 95 %                            |
| sides  | 2-sided                         |
| lower limit  | 1                               |
| upper limit  | 1.48                            |

### Secondary: 7 day point prevalence abstinence at 4 weeks

|  |  |
|--|--|
| End point title  | 7 day point prevalence abstinence at 4 weeks |
| End point description:<br>point prevalence abstinence at 4 weeks after quit date |  |
| End point type   | Secondary                                    |
| End point timeframe:<br>4 weeks after quit date                                  |  |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | preloading      | control         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 899             | 893             |  |  |
| Units: 0 1                  |                 |                 |  |  |
| no                          | 580             | 605             |  |  |
| yes                         | 319             | 288             |  |  |

### Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | 7 day point prevalence abstinence at 4 weeks |
| Statistical analysis description:<br>logistic regression adjusted for centre |  |
| Comparison groups  | preloading v control                         |
| Number of subjects included in analysis                                      | 1792   |
| Analysis specification   | Pre-specified                                |
| Analysis type  | superiority                                  |
| P-value  | = 0.149                                      |
| Method   | Regression, Logistic                         |
| Parameter estimate   | Odds ratio (OR)                              |
| Point estimate   | 1.16   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided                                      |
| lower limit  | 0.95   |
| upper limit  | 1.41   |

### Secondary: 7 day point prevalence abstinence at 6 months

|   |   |
|---|---|
| End point title   | 7 day point prevalence abstinence at 6 months |
| End point description:<br>7 day point prevalence abstinence at 6 months after quit date |   |
| End point type  | Secondary                                     |
| End point timeframe:<br>6 months after quit date  |   |

| End point values            | preloading      | control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 899             | 893             |  |  |
| Units: 0 1                  |                 |                 |  |  |
| no                          | 699             | 712             |  |  |
| yes                         | 200             | 181             |  |  |

## Statistical analyses

| Statistical analysis title   | 7 day point prevalence abstinence at 6 months |
|--|---|
| Statistical analysis description:<br>logistic regression adjusted for centre |   |
| Comparison groups  | preloading v control                          |
| Number of subjects included in analysis                                      | 1792  |
| Analysis specification   | Pre-specified                                 |
| Analysis type  | superiority                                   |
| P-value  | = 0.306                                       |
| Method   | Regression, Logistic                          |
| Parameter estimate   | Odds ratio (OR)                               |
| Point estimate   | 1.13  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided                                       |
| lower limit  | 0.9   |
| upper limit  | 1.41  |

## Secondary: 12 months validated abstinence

| End point title  | 12 months validated abstinence |
|--|--------------------------------|
| End point description:<br>12 months validated abstinence after quit date |                                |
| End point type   | Secondary                      |
| End point timeframe:<br>12 months after quit date                        |                                |

| End point values            | preloading      | control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 899             | 893             |  |  |
| Units: 0 1                  |                 |                 |  |  |
| no                          | 773             | 792             |  |  |
| yes                         | 126             | 101             |  |  |

## Statistical analyses

|  |                                |
|--|--------------------------------|
| <b>Statistical analysis title</b>  | 12 months validated abstinence |
| Statistical analysis description:<br>logistic regression adjusted for centre |                                |
| Comparison groups  | preloading v control           |
| Number of subjects included in analysis                                      | 1792                           |
| Analysis specification   | Pre-specified                  |
| Analysis type  | superiority                    |
| P-value  | = 0.085                        |
| Method   | Regression, Logistic           |
| Parameter estimate   | Odds ratio (OR)                |
| Point estimate   | 1.28                           |
| Confidence interval  |                                |
| level  | 95 %                           |
| sides  | 2-sided                        |
| lower limit  | 0.97                           |
| upper limit  | 1.69                           |

## Secondary: 7 day point prevalence abstinence at 12 months

|   |  |
|---|--|
| End point title   | 7 day point prevalence abstinence at 12 months |
| End point description:<br>7 day point prevalence abstinence 12 months after quit date |  |
| End point type  | Secondary                                      |
| End point timeframe:<br>12 months after quit date                                     |  |

| End point values            | preloading      | control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 899             | 893             |  |  |
| Units: 0 1                  |                 |                 |  |  |
| no                          | 698             | 723             |  |  |
| yes                         | 201             | 170             |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | 7 day point prevalence abstinence at 12 months |
| Statistical analysis description:<br>logistic regression with adjustment for centre |  |
| Comparison groups   | preloading v control                           |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 1792                 |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| P-value                                 | = 0.082              |
| Method                                  | Regression, Logistic |
| Parameter estimate                      | Odds ratio (OR)      |
| Point estimate                          | 1.23                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 0.97                 |
| upper limit                             | 1.54                 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

adverse events are those that occurred after baseline and until one week after quit day. In the protocol, we deemed that we would report only adverse events of moderate severity or above i.e. those that hindered normal activities

Adverse event reporting additional description:

we elicited adverse events from participants in both arms at contacts -3 weeks (one week after baseline) and at +1 week (five weeks after baseline and one week after quit day).

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | preloading |
|-----------------------|------------|

Reporting group description:

In the intervention arm, participants wore a 21mg nicotine patch daily for an intended four weeks prior to quit day.

|                       |         |
|-----------------------|---------|
| Reporting group title | control |
|-----------------------|---------|

Reporting group description:

standard smoking cessation support only

| Serious adverse events                            | preloading      | control         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 8 / 899 (0.89%) | 8 / 893 (0.90%) |  |
| number of deaths (all causes)                     | 2               | 2               |  |
| number of deaths resulting from adverse events    | 2               | 2               |  |
| Investigations                                    |                 |                 |  |
| Aspiration pleural cavity                         |                 |                 |  |
| subjects affected / exposed                       | 1 / 899 (0.11%) | 0 / 893 (0.00%) |  |
| occurrences causally related to treatment / all   | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 1 / 1           | 0 / 0           |  |
| Injury, poisoning and procedural complications    |                 |                 |  |
| Accident  |                 |                 |  |
| subjects affected / exposed                       | 0 / 899 (0.00%) | 1 / 893 (0.11%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 1           |  |
| Cardiac disorders                                 |                 |                 |  |
| Acute coronary syndrome                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 899 (0.22%) | 0 / 893 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Hernia repair                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 899 (0.00%) | 1 / 893 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 899 (0.11%) | 0 / 893 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Oesophageal carcinoma                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 899 (0.00%) | 1 / 893 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 899 (0.00%) | 1 / 893 (0.11%) |  |
| 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 |                 |                 |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 899 (0.11%) | 1 / 893 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 0 / 899 (0.00%) | 2 / 893 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Psychiatric disorders                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Psychotic disorder                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 899 (0.11%) | 0 / 893 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Intentional self-injury                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 899 (0.11%) | 0 / 893 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 899 (0.00%) | 1 / 893 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Pelvic fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 899 (0.11%) | 0 / 893 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 0.5 %

| <b>Non-serious adverse events</b>                     | preloading         | control          |  |
|---|--------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                    |                  |  |
| subjects affected / exposed                           | 139 / 899 (15.46%) | 85 / 893 (9.52%) |  |
| Injury, poisoning and procedural complications        |                    |                  |  |
| Injury  |                    |                  |  |
| subjects affected / exposed                           | 4 / 899 (0.44%)    | 8 / 893 (0.90%)  |  |
| occurrences (all)                                     | 4                  | 8                |  |
| Nervous system disorders                              |                    |                  |  |
| Abnormal dreams                                       |                    |                  |  |
| subjects affected / exposed                           | 9 / 899 (1.00%)    | 1 / 893 (0.11%)  |  |
| occurrences (all)                                     | 9                  | 1                |  |
| Dizziness   |                    |                  |  |
| subjects affected / exposed                           | 15 / 899 (1.67%)   | 6 / 893 (0.67%)  |  |
| occurrences (all)                                     | 15                 | 6                |  |



|  |                        |                      |  |
|--|------------------------|----------------------|--|
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 14 / 899 (1.56%)<br>14 | 3 / 893 (0.34%)<br>3 |  |
| Poor quality sleep<br>subjects affected / exposed<br>occurrences (all)   | 20 / 899 (2.22%)<br>20 | 3 / 893 (0.34%)<br>3 |  |
| General disorders and administration site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 10 / 899 (1.11%)<br>10 | 5 / 893 (0.56%)<br>5 |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 6 / 899 (0.67%)<br>6   | 0 / 893 (0.00%)<br>0 |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                     | 6 / 899 (0.67%)<br>6   | 3 / 893 (0.34%)<br>3 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 8 / 899 (0.89%)<br>8   | 3 / 893 (0.34%)<br>3 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 30 / 899 (3.34%)<br>30 | 8 / 893 (0.90%)<br>8 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 14 / 899 (1.56%)<br>14 | 3 / 893 (0.34%)<br>3 |  |
| Respiratory, thoracic and mediastinal disorders<br>Infection<br>subjects affected / exposed<br>occurrences (all)     | 1 / 899 (0.11%)<br>1   | 4 / 893 (0.45%)<br>4 |  |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)   | 7 / 899 (0.78%)<br>7   | 3 / 893 (0.34%)<br>3 |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 4 / 899 (0.44%)<br>4   | 7 / 893 (0.78%)<br>7 |  |

|   |                        |                      |  |
|---|------------------------|----------------------|--|
| Skin and subcutaneous tissue disorders<br>Skin irritation<br>subjects affected / exposed<br>occurrences (all)                   | 5 / 899 (0.56%)<br>5   | 2 / 893 (0.22%)<br>2 |  |
| Psychiatric disorders<br>Depressed mood<br>subjects affected / exposed<br>occurrences (all)                                     | 5 / 899 (0.56%)<br>5   | 4 / 893 (0.45%)<br>4 |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal disorder<br>subjects affected / exposed<br>occurrences (all) | 10 / 899 (1.11%)<br>10 | 7 / 893 (0.78%)<br>7 |  |

## **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