



## Clinical trial results:

**A phase III trial evaluating the role of ovarian function suppression and the role of exemestane as adjuvant therapies for premenopausal women with endocrine responsive breast cancer.**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2004-000166-13    |
| Trial protocol           | DK SE DE ES IE HU |
| Global end of trial date |                   |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 05 May 2021  |
| First version publication date | 05 May 2021  |

### Trial information

#### Trial identification

|                       |                           |
|-----------------------|---------------------------|
| Sponsor protocol code | IBCSG 24-02 BIG 2-02 SOFT |
|-----------------------|---------------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00066690 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | IBCSG  |
| Sponsor organisation address | Effingerstrasse 40, Bern, Switzerland, 3008  |
| Public contact               | IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 31 511 94 00, <a href="mailto:regulatoryoffice@ibcsg.org">regulatoryoffice@ibcsg.org</a> |
| Scientific contact           | IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 31 511 94 00, <a href="mailto:regulatoryoffice@ibcsg.org">regulatoryoffice@ibcsg.org</a> |

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                                       | Interim       |
| Date of interim/final analysis                       | 31 March 2014 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 31 March 2014 |
| Global end of trial reached?                         | No            |

Notes:

## General information about the trial

Main objective of the trial:

This trial will evaluate the worth of ovarian function suppression (achieved by either long-term use of GnRH analogue or surgical oophorectomy or ovarian irradiation) plus tamoxifen compared with tamoxifen alone for premenopausal women with steroid hormone receptor positive early invasive breast cancer who either receive no adjuvant chemotherapy or remain premenopausal following adjuvant and/or neoadjuvant chemotherapy. In addition, the worth of exemestane will be evaluated for this premenopausal patient population by comparing ovarian function suppression plus exemestane with tamoxifen alone and by comparing ovarian function suppression plus exemestane with ovarian function suppression plus tamoxifen.

Protection of trial subjects:

In compliance with GDPR.

Adverse events were reported and in case of adverse events and treatment-related toxicities management guidance was provided in the study protocol to treat trial subjects in adequately manner. The safety of the trial treatment was regularly reviewed by the IBCSG Data Safety Monitoring Committee (DSMC).

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 04 August 2003   |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 11 Years         |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 74 |
| Country: Number of subjects enrolled | Australia: 182     |
| Country: Number of subjects enrolled | New Zealand: 58    |
| Country: Number of subjects enrolled | Brazil: 6          |
| Country: Number of subjects enrolled | Chile: 72          |
| Country: Number of subjects enrolled | India: 52          |
| Country: Number of subjects enrolled | Italy: 288         |
| Country: Number of subjects enrolled | Peru: 53           |
| Country: Number of subjects enrolled | Switzerland: 114   |
| Country: Number of subjects enrolled | South Africa: 13   |
| Country: Number of subjects enrolled | Belgium: 122       |
| Country: Number of subjects enrolled | Israel: 8          |
| Country: Number of subjects enrolled | Netherlands: 11    |

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Turkey: 17          |
| Country: Number of subjects enrolled | Poland: 2           |
| Country: Number of subjects enrolled | Serbia: 9           |
| Country: Number of subjects enrolled | United States: 1030 |
| Country: Number of subjects enrolled | Portugal: 31        |
| Country: Number of subjects enrolled | Spain: 451          |
| Country: Number of subjects enrolled | Sweden: 62          |
| Country: Number of subjects enrolled | France: 194         |
| Country: Number of subjects enrolled | Germany: 54         |
| Country: Number of subjects enrolled | Hungary: 150        |
| Country: Number of subjects enrolled | Ireland: 13         |
| Worldwide total number of subjects   | 3066                |
| EEA total number of subjects         | 1452                |

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)                      | 3066 |
| From 65 to 84 years                       | 0    |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details:

3066 patients were randomized between 17Dec03 and 27Jan11 at 426 centers in 25 countries.

### Pre-assignment

Screening details:

This trial used a web-based randomization system. Each Participating Group determined how its Participating Centers will access the randomization system, either through a Group Randomization Center, or directly from the Participating Center.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Overall study           |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

### Arms

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

Arm description:

Tamoxifen 20mg orally daily for 5 years

|  |   |
|--|---|
| Arm type                               | Active comparator   |
| Investigational medicinal product name | Tamoxifen   |
| Investigational medicinal product code |   |
| Other name                             | Apo-Tamox, Clonoxifen, Dignotamoxi, Ebefen, Emblon, Estroxyn, Fentamox, Gen-Tamoxifen, Genox, ICI 46.474, ICI-46474, Jenoxifen, Kessar, Ledertam, Lesporene |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

Dosage and administration details:

Tamoxifen 20mg orally daily for 5 years

|                  |       |
|------------------|-------|
| <b>Arm title</b> | T+OFS |
|------------------|-------|

Arm description:

Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Tamoxifen   |
| Investigational medicinal product code |   |
| Other name                             | Apo-Tamox, Clonoxifen, Dignotamoxi, Ebefen, Emblon, Estroxyn, Fentamox, Gen-Tamoxifen, Genox, ICI 46.474, ICI-46474, Jenoxifen, Kessar, Ledertam, Lesporene |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

Dosage and administration details:

Tamoxifen 20mg orally daily for 5 years

|  |  |
|--|--|
| Investigational medicinal product name | Triptorelin  |
| Investigational medicinal product code |  |
| Other name                             | 6-D-Tryptophan-LH-RH, 6-D-Tryptophanluteinizing Hormone-releasing Factor, AY-25650, CL-118532, Decapeptyl, Detryptoreline, GnRH analogue, Trelstar Depot, Decape |
| Pharmaceutical forms                   | Injection  |

|                          |                 |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

3.75 mg by im injection q28 days for 5 years

|                  |         |
|------------------|---------|
| <b>Arm title</b> | E + OFS |
|------------------|---------|

Arm description:

Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Exemestane          |
| Investigational medicinal product code |                     |
| Other name                             | Aromasin, FCE-24304 |
| Pharmaceutical forms                   | Coated tablet       |
| Routes of administration               | Oral use            |

Dosage and administration details:

25mg orally daily for 5 years

|  |  |
|--|--|
| Investigational medicinal product name | Triptorelin  |
| Investigational medicinal product code |  |
| Other name                             | 6-D-Tryptophan-LH-RH, 6-D-Tryptophanluteinizing Hormone-releasing Factor, AY-25650, CL-118532, Decapeptyl, Detryptoreline, GnRH analogue, Trelstar Depot, Decape |
| Pharmaceutical forms                   | Injection  |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

3.75 mg by im injection q28 days for 5 years

| Number of subjects in period 1 | Tamoxifen | T+OFS | E + OFS |
|--------------------------------|-----------|-------|---------|
| Started                        | 1021      | 1024  | 1021    |
| Completed                      | 1018      | 1015  | 1014    |
| Not completed                  | 3         | 9     | 7       |
| Consent withdrawn by subject   | 3         | 9     | 7       |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | ITT analysis            |
| Is this the baseline period? | Yes <sup>[1]</sup>      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

## Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|  |  |
|--|--|
| <b>Arm title</b>   | Tamoxifen  |
| Arm description:<br>Tamoxifen 20mg orally daily for 5 years  |  |
| Arm type   | Active comparator  |
| Investigational medicinal product name   | Tamoxifen  |
| Investigational medicinal product code   |  |
| Other name   | Apo-Tamox, Clonoxifen, Dignotamoxi, Ebefen, Emblon, Estroxyn, Fentamox, Gen-Tamoxifen, Genox, ICI 46.474, ICI-46474, Jenoxifen, Kessar, Ledertam, Lesporene      |
| Pharmaceutical forms   | Tablet   |
| Routes of administration   | Oral use   |
| Dosage and administration details:<br>Tamoxifen 20mg orally daily for 5 years  |  |
| <b>Arm title</b>   | T+OFS  |
| Arm description:<br>Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)  |  |
| Arm type   | Experimental   |
| Investigational medicinal product name   | Tamoxifen  |
| Investigational medicinal product code   |  |
| Other name   | Apo-Tamox, Clonoxifen, Dignotamoxi, Ebefen, Emblon, Estroxyn, Fentamox, Gen-Tamoxifen, Genox, ICI 46.474, ICI-46474, Jenoxifen, Kessar, Ledertam, Lesporene      |
| Pharmaceutical forms   | Tablet   |
| Routes of administration   | Oral use   |
| Dosage and administration details:<br>Tamoxifen 20mg orally daily for 5 years  |  |
| Investigational medicinal product name   | Triptorelin  |
| Investigational medicinal product code   |  |
| Other name   | 6-D-Tryptophan-LH-RH, 6-D-Tryptophanluteinizing Hormone-releasing Factor, AY-25650, CL-118532, Decapeptyl, Detryptoreline, GnRH analogue, Trelstar Depot, Decape |
| Pharmaceutical forms   | Injection  |
| Routes of administration   | Intravenous use  |
| Dosage and administration details:<br>3.75 mg by im injection q28 days for 5 years   |  |
| <b>Arm title</b>   | E + OFS  |
| Arm description:<br>Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation) |  |
| Arm type   | Experimental   |
| Investigational medicinal product name   | Exemestane   |
| Investigational medicinal product code   |  |
| Other name   | Aromasin, FCE-24304  |
| Pharmaceutical forms   | Coated tablet  |
| Routes of administration   | Oral use   |
| Dosage and administration details:<br>25mg orally daily for 5 years  |  |
| Investigational medicinal product name   | Triptorelin  |
| Investigational medicinal product code   |  |
| Other name   | 6-D-Tryptophan-LH-RH, 6-D-Tryptophanluteinizing Hormone-releasing Factor, AY-25650, CL-118532, Decapeptyl,   |

|                          |   |
|--------------------------|---|
|                          | Detryptoreline, GnRH analogue, Trelstar Depot, Decape |
| Pharmaceutical forms     | Injection   |
| Routes of administration | Intravenous use                                       |

Dosage and administration details:

3.75 mg by im injection q28 days for 5 years

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics were only reported for Intention-to-treat population

| <b>Number of subjects in period 2<sup>[2]</sup></b> | Tamoxifen | T+OFS | E + OFS |
|---|-----------|-------|---------|
| Started   | 1018      | 1015  | 1014    |
| Completed   | 1018      | 1015  | 1014    |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Intention-to-treat population, excludes 19 patients who immediately withdrew consent.

## Baseline characteristics

### Reporting groups

|  |           |
|--|-----------|
| Reporting group title  | Tamoxifen |
| Reporting group description:<br>Tamoxifen 20mg orally daily for 5 years  |           |
| Reporting group title  | T+OFS     |
| Reporting group description:<br>Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)  |           |
| Reporting group title  | E + OFS   |
| Reporting group description:<br>Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation) |           |

| Reporting group values  | Tamoxifen | T+OFS    | E + OFS  |
|---|-----------|----------|----------|
| Number of subjects  | 1018      | 1015     | 1014     |
| Age categorical<br>Units: Subjects  |           |          |          |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>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 |           |          |          |
| Age continuous<br>Units: years  |           |          |          |
| median  | 43        | 43       | 43       |
| inter-quartile range (Q1-Q3)  | 38 to 46  | 38 to 47 | 38 to 47 |
| Gender categorical<br>Units: Subjects   |           |          |          |
| Female  | 1018      | 1015     | 1014     |
| Male  | 0         | 0        | 0        |
| Race/Ethnicity<br>Units: Subjects   |           |          |          |
| American Indian/Alaskan native  | 1         | 5        | 3        |
| Asian   | 36        | 34       | 33       |
| Black/African American  | 32        | 27       | 34       |
| Hawaiian/Pacific Islander   | 5         | 4        | 3        |
| White/Caucasian   | 877       | 873      | 866      |
| Other   | 4         | 2        | 3        |
| Unknown   | 19        | 22       | 22       |
| Hispanic/Latino/South American native   | 44        | 48       | 50       |



|  |       |  |  |
|--|-------|--|--|
| <b>Reporting group values</b>  | Total |  |  |
| Number of subjects   | 3047  |  |  |
| Age categorical<br>Units: Subjects                                       |       |  |  |
| In utero   | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks)                    | 0     |  |  |
| Newborns (0-27 days)   | 0     |  |  |
| Infants and toddlers (28 days-23<br>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<br>Units: years<br>median<br>inter-quartile range (Q1-Q3) | -     |  |  |
| Gender categorical<br>Units: Subjects                                    |       |  |  |
| Female   | 3047  |  |  |
| Male   | 0     |  |  |
| Race/Ethnicity<br>Units: Subjects  |       |  |  |
| American Indian/Alaskan native   | 9     |  |  |
| Asian  | 103   |  |  |
| Black/African American   | 93    |  |  |
| Hawaiian/Pacific Islander  | 12    |  |  |
| White/Caucasian  | 2616  |  |  |
| Other  | 9     |  |  |
| Unknown  | 63    |  |  |
| Hispanic/Latino/South American<br>native                                 | 142   |  |  |

## End points

### End points reporting groups

|  |           |
|--|-----------|
| Reporting group title  | Tamoxifen |
| Reporting group description:<br>Tamoxifen 20mg orally daily for 5 years  |           |
| Reporting group title  | T+OFS     |
| Reporting group description:<br>Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)  |           |
| Reporting group title  | E + OFS   |
| Reporting group description:<br>Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation) |           |
| Reporting group title  | Tamoxifen |
| Reporting group description:<br>Tamoxifen 20mg orally daily for 5 years  |           |
| Reporting group title  | T+OFS     |
| Reporting group description:<br>Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)  |           |
| Reporting group title  | E + OFS   |
| Reporting group description:<br>Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation) |           |

### Primary: Disease-free Survival

|   |                       |
|---|-----------------------|
| End point title   | Disease-free Survival |
| End point description:<br>Estimated percentage of patients alive and disease-free at 5 years from randomization, where disease-free survival is defined as the time from randomization to the first appearance of one of the following: invasive breast cancer recurrence at local, regional, or distant site, invasive contralateral breast cancer, second (non-breast) invasive cancer, or death without cancer event; or censored at date of last follow-up. |                       |
| End point type  | Primary               |
| End point timeframe:<br>5-year estimates, reported at a median follow-up of 67 months.  |                       |

| End point values                  | Tamoxifen           | T+OFS               | E + OFS           |  |
|-----------------------------------|---------------------|---------------------|-------------------|--|
| Subject group type                | Reporting group     | Reporting group     | Reporting group   |  |
| Number of subjects analysed       | 1018                | 1015                | 1014              |  |
| Units: Percentage of participants |                     |                     |                   |  |
| number (confidence interval 95%)  | 84.7 (82.2 to 86.9) | 86.6 (84.2 to 88.7) | 89 (86.8 to 90.9) |  |

## Statistical analyses

|   |                        |
|---|------------------------|
| <b>Statistical analysis title</b>                     | Statistical analysis 1 |
| Statistical analysis description:<br>Tamoxifen, T+OFS |                        |
| Comparison groups                                     | Tamoxifen v T+OFS      |
| Number of subjects included in analysis               | 2033                   |
| Analysis specification                                | Pre-specified          |
| Analysis type   | superiority            |
| P-value   | = 0.1                  |
| Method  | Logrank                |
| Parameter estimate                                    | Hazard ratio (HR)      |
| Point estimate  | 0.83                   |
| Confidence interval                                   |                        |
| level   | 95 %                   |
| sides   | 2-sided                |
| lower limit   | 0.66                   |
| upper limit   | 1.04                   |

|   |                        |
|---|------------------------|
| <b>Statistical analysis title</b>                     | Statistical analysis 2 |
| Statistical analysis description:<br>Tamoxifen, E+OFS |                        |
| Comparison groups                                     | Tamoxifen v E + OFS    |
| Number of subjects included in analysis               | 2032                   |
| Analysis specification                                | Pre-specified          |
| Analysis type   | superiority            |
| Parameter estimate                                    | Hazard ratio (HR)      |
| Point estimate  | 0.68                   |
| Confidence interval                                   |                        |
| level   | 95 %                   |
| sides   | 2-sided                |
| lower limit   | 0.53                   |
| upper limit   | 0.86                   |

## Secondary: Breast Cancer-free Interval

|                 |                             |
|-----------------|-----------------------------|
| End point title | Breast Cancer-free Interval |
|-----------------|-----------------------------|

End point description:

Estimated percentage of patients alive and disease-free at 5 years from randomization, where breast cancer-free interval is defined as the time from randomization to invasive breast cancer recurrence at local, regional, or distant site, or invasive contralateral breast cancer; or censored at date of last follow up.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| 5-year estimates, reported at a median follow-up of 67 months. |           |

| End point values                  | Tamoxifen           | T+OFS               | E + OFS             |  |
|-----------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed       | 1018                | 1015                | 1014                |  |
| Units: Percentage of participants |                     |                     |                     |  |
| number (confidence interval 85%)  | 86.4 (84.0 to 88.5) | 88.4 (86.1 to 90.3) | 90.9 (88.9 to 92.6) |  |

## Statistical analyses

| Statistical analysis title              | Statistical analysis 1 |
|---|------------------------|
| Statistical analysis description:       |                        |
| Tamoxifen, T+OFS                        |                        |
| Comparison groups                       | Tamoxifen v T+OFS      |
| Number of subjects included in analysis | 2033                   |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.09                 |
| Method                                  | Logrank                |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.81                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.3                    |
| upper limit                             | 1.03                   |

| Statistical analysis title              | Statistical analysis 2 |
|---|------------------------|
| Statistical analysis description:       |                        |
| Tamoxifen, E+OFS                        |                        |
| Comparison groups                       | Tamoxifen v E + OFS    |
| Number of subjects included in analysis | 2032                   |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.64                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.49                   |
| upper limit                             | 0.83                   |

## Secondary: Distant Recurrence-free Interval

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Distant Recurrence-free Interval |
|-----------------|----------------------------------|

End point description:

Estimated percentage of patients alive and disease-free at 5 years from randomization, where distant recurrence-free Interval is defined as the time from randomization to invasive breast cancer recurrence at distant site, or invasive contralateral breast cancer; or censored at date of last follow up.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5-year estimates, reported at a median follow-up of 67 months.

| End point values                  | Tamoxifen           | T+OFS               | E + OFS             |  |
|-----------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed       | 1018                | 1015                | 1014                |  |
| Units: Percentage of participants |                     |                     |                     |  |
| number (confidence interval 95%)  | 90.7 (88.6 to 92.4) | 91.3 (89.2 to 92.9) | 93.0 (91.2 to 94.5) |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Tamoxifen, T+OFS

|                   |                   |
|-------------------|-------------------|
| Comparison groups | Tamoxifen v T+OFS |
|-------------------|-------------------|

|   |      |
|---|------|
| Number of subjects included in analysis | 2033 |
|---|------|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |             |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

|         |       |
|---------|-------|
| P-value | = 0.4 |
|---------|-------|

|        |         |
|--------|---------|
| Method | Logrank |
|--------|---------|

|                    |                   |
|--------------------|-------------------|
| Parameter estimate | Hazard ratio (HR) |
|--------------------|-------------------|

|                |      |
|----------------|------|
| Point estimate | 0.88 |
|----------------|------|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 0.66 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 1.18 |
|-------------|------|

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

Tamoxifen, E+OFS

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Tamoxifen v E + OFS |
|-------------------|---------------------|

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 2032              |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.71              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.52              |
| upper limit                             | 0.96              |

## Secondary: Overall Survival

|   |                  |
|---|------------------|
| End point title   | Overall Survival |
| End point description:  |                  |
| Estimated percentage of patients alive at 8 years from randomization, where overall survival is defined as the time from randomization to death from any cause; or censored at date last known alive. |                  |
| End point type  | Secondary        |
| End point timeframe:  |                  |
| 8-year estimates, reported at a median follow-up of 8 years   |                  |

| End point values                  | Tamoxifen           | T+OFS               | E + OFS             |  |
|-----------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed       | 1018                | 1015                | 1014                |  |
| Units: Percentage of participants |                     |                     |                     |  |
| number (confidence interval 95%)  | 91.5 (89.4 to 93.2) | 93.3 (91.4 to 94.8) | 92.1 (90.0 to 93.7) |  |

## Statistical analyses

|   |                        |
|---|------------------------|
| Statistical analysis title              | Statistical analysis 1 |
| Statistical analysis description:       |                        |
| Tamoxifen, T+OFS                        |                        |
| Comparison groups                       | Tamoxifen v T+OFS      |
| Number of subjects included in analysis | 2033                   |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.01                 |
| Method                                  | Logrank                |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.67                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.48    |
| upper limit         | 0.92    |

|   |                        |
|---|------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 2 |
| Comparison groups                       | Tamoxifen v E + OFS    |
| Number of subjects included in analysis | 2032                   |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.85                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.62                   |
| upper limit                             | 1.15                   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Assessed every 3 months for the first year, then every 6 month until year 6. Reported at a median follow-up of 67 months.

Adverse event reporting additional description:

Targeted AEs and other grade 3 or higher AEs were collected on CRFs, regardless of attribution. The safety population EXCLUDES patients who never started protocol-assigned therapy.

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

### Dictionary used

|                 |           |
|-----------------|-----------|
| Dictionary name | NCI CTCAE |
|-----------------|-----------|

|                    |     |
|--------------------|-----|
| Dictionary version | 3.0 |
|--------------------|-----|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Tamoxifen |
|-----------------------|-----------|

Reporting group description:

The safety population EXCLUDES patients who never started protocol-assigned therapy.

|                       |       |
|-----------------------|-------|
| Reporting group title | T+OFS |
|-----------------------|-------|

Reporting group description:

The safety population EXCLUDES patients who never started protocol-assigned therapy.

|                       |       |
|-----------------------|-------|
| Reporting group title | E+OFS |
|-----------------------|-------|

Reporting group description: -

| Serious adverse events  | Tamoxifen              | T+OFS                  | E+OFS                  |
|---|------------------------|------------------------|------------------------|
| Total subjects affected by serious adverse events                       |                        |                        |                        |
| subjects affected / exposed   | 315 / 1007<br>(31.28%) | 375 / 1007<br>(37.24%) | 375 / 1001<br>(37.46%) |
| number of deaths (all causes)   | 3                      | 0                      | 3                      |
| number of deaths resulting from adverse events                          |                        |                        |                        |
| Vascular disorders  |                        |                        |                        |
| Postoperative bleeding (breast reconstruction) leading to severe anemia |                        |                        |                        |
| subjects affected / exposed   | 0 / 1007 (0.00%)       | 0 / 1007 (0.00%)       | 1 / 1001 (0.10%)       |
| occurrences causally related to treatment / all                         | 0 / 0                  | 0 / 0                  | 0 / 1                  |
| deaths causally related to treatment / all                              | 0 / 3                  | 0 / 0                  | 0 / 3                  |
| Subarachnoidale hemorrhage  |                        |                        |                        |
| subjects affected / exposed   | 0 / 1007 (0.00%)       | 0 / 1007 (0.00%)       | 1 / 1001 (0.10%)       |
| occurrences causally related to treatment / all                         | 0 / 0                  | 0 / 0                  | 0 / 1                  |
| deaths causally related to treatment / all                              | 0 / 3                  | 0 / 0                  | 0 / 3                  |
| Central vein thrombosis (L eye)   |                        |                        |                        |



|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| subjects affected / exposed                       | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0             | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all        | 0 / 3             | 0 / 0            | 0 / 3            |
| Deep Vein Thrombosis                              |                   |                  |                  |
| subjects affected / exposed                       | 10 / 1007 (0.99%) | 6 / 1007 (0.60%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all   | 10 / 10           | 6 / 6            | 1 / 1            |
| deaths causally related to treatment / all        | 0 / 3             | 0 / 0            | 0 / 3            |
| Ischemic Necrosis of Ileum and Jejunum            |                   |                  |                  |
| subjects affected / exposed                       | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all        | 0 / 3             | 0 / 0            | 0 / 3            |
| Peripheral arterial ischemia                      |                   |                  |                  |
| subjects affected / exposed                       | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0             | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all        | 0 / 3             | 0 / 0            | 0 / 3            |
| Pulmonary Embolism                                |                   |                  |                  |
| subjects affected / exposed                       | 1 / 1007 (0.10%)  | 3 / 1007 (0.30%) | 3 / 1001 (0.30%) |
| occurrences causally related to treatment / all   | 1 / 1             | 3 / 3            | 2 / 3            |
| deaths causally related to treatment / all        | 0 / 3             | 0 / 0            | 0 / 3            |
| Superficial Vein Thrombosis                       |                   |                  |                  |
| subjects affected / exposed                       | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all   | 0 / 0             | 1 / 1            | 2 / 2            |
| deaths causally related to treatment / all        | 0 / 3             | 0 / 0            | 0 / 3            |
| Thrombosis  |                   |                  |                  |
| subjects affected / exposed                       | 2 / 1007 (0.20%)  | 2 / 1007 (0.20%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all   | 1 / 2             | 2 / 2            | 1 / 1            |
| deaths causally related to treatment / all        | 0 / 3             | 0 / 0            | 0 / 3            |
| Surgical and medical procedures                   |                   |                  |                  |
| Induced/elective abortion 8 weeks in to pregnancy |                   |                  |                  |
| subjects affected / exposed                       | 1 / 1007 (0.10%)  | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all   | 1 / 1             | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all        | 0 / 3             | 0 / 0            | 0 / 3            |
| Pregnancy, puerperium and perinatal               |                   |                  |                  |

|  |                  |                  |                  |
|--|------------------|------------------|------------------|
| conditions   |                  |                  |                  |
| Pregnancy  |                  |                  |                  |
| subjects affected / exposed                          | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 3            | 0 / 0            | 0 / 3            |
| General disorders and administration site conditions |                  |                  |                  |
| Fatigue (asthenia, lethargy, malaise)                |                  |                  |                  |
| subjects affected / exposed                          | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 3            | 0 / 0            | 0 / 3            |
| Insomnia   |                  |                  |                  |
| subjects affected / exposed                          | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 3            | 0 / 0            | 0 / 3            |
| Obesity  |                  |                  |                  |
| subjects affected / exposed                          | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all           | 0 / 3            | 0 / 0            | 0 / 3            |
| Postoperative fever (in the absence of neutropenia)  |                  |                  |                  |
| subjects affected / exposed                          | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0            | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 3            | 0 / 0            | 0 / 3            |
| Immune system disorders                              |                  |                  |                  |
| Allergic reaction                                    |                  |                  |                  |
| subjects affected / exposed                          | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 3 / 1001 (0.30%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0            | 1 / 3            |
| deaths causally related to treatment / all           | 0 / 3            | 0 / 0            | 0 / 3            |
| Reproductive system and breast disorders             |                  |                  |                  |
| Pain Left Breast                                     |                  |                  |                  |
| subjects affected / exposed                          | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 3            | 0 / 0            | 0 / 3            |
| Adnexal and Ovarian Lesion                           |                  |                  |                  |

|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1007 (0.10%)  | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            | 0 / 3            |
| Cervical Polyp                                  |                   |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            | 0 / 3            |
| Cervical Dysplasia                              |                   |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            | 0 / 3            |
| Endometrial Hyperplasia                         |                   |                  |                  |
| subjects affected / exposed                     | 15 / 1007 (1.49%) | 6 / 1007 (0.60%) | 5 / 1001 (0.50%) |
| occurrences causally related to treatment / all | 15 / 15           | 5 / 6            | 4 / 5            |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            | 0 / 3            |
| Endometrial Polyp                               |                   |                  |                  |
| subjects affected / exposed                     | 8 / 1007 (0.79%)  | 3 / 1007 (0.30%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 9 / 9             | 3 / 3            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            | 0 / 3            |
| High grade squamous intraepithelial lesion      |                   |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%)  | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            | 0 / 3            |
| Intramural leiomyoma leading to hemorrhage      |                   |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            | 0 / 3            |
| Irregular Menses                                |                   |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%)  | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1             | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            | 0 / 3            |
| Ovarian Cyst                                    |                   |                  |                  |

|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| subjects affected / exposed                             | 24 / 1007 (2.38%) | 2 / 1007 (0.20%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all         | 26 / 26           | 2 / 2            | 0 / 2            |
| deaths causally related to treatment / all              | 0 / 3             | 0 / 0            | 0 / 3            |
| Uterine Adenomyosis                                     |                   |                  |                  |
| subjects affected / exposed                             | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all         | 0 / 0             | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all              | 0 / 3             | 0 / 0            | 0 / 3            |
| Uterine Fibroma   |                   |                  |                  |
| subjects affected / exposed                             | 5 / 1007 (0.50%)  | 3 / 1007 (0.30%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all         | 3 / 5             | 3 / 3            | 1 / 1            |
| deaths causally related to treatment / all              | 0 / 3             | 0 / 0            | 0 / 3            |
| Uterine Myoma   |                   |                  |                  |
| subjects affected / exposed                             | 2 / 1007 (0.20%)  | 2 / 1007 (0.20%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all         | 2 / 2             | 2 / 2            | 0 / 0            |
| deaths causally related to treatment / all              | 0 / 3             | 0 / 0            | 0 / 3            |
| Uterine Polyp   |                   |                  |                  |
| subjects affected / exposed                             | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all         | 0 / 0             | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all              | 0 / 3             | 0 / 0            | 0 / 3            |
| Uterine prolapse  |                   |                  |                  |
| subjects affected / exposed                             | 1 / 1007 (0.10%)  | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all         | 0 / 1             | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all              | 0 / 3             | 0 / 0            | 0 / 3            |
| Vaginal Bleeding  |                   |                  |                  |
| subjects affected / exposed                             | 8 / 1007 (0.79%)  | 2 / 1007 (0.20%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all         | 6 / 8             | 2 / 2            | 1 / 1            |
| deaths causally related to treatment / all              | 0 / 3             | 0 / 0            | 0 / 3            |
| Atypical Ductal Hyperplasia and Fibroadenoma (R Breast) |                   |                  |                  |
| subjects affected / exposed                             | 0 / 1007 (0.00%)  | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all         | 0 / 0             | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all              | 0 / 3             | 0 / 0            | 0 / 3            |
| Benign fibroadenoma R breast                            |                   |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Respiratory, thoracic and mediastinal disorders |                  |                  |                  |
| Atypical pleuritic pain                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Chest Pain                                      |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1007 (0.30%) | 4 / 1007 (0.40%) | 6 / 1001 (0.60%) |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 4            | 1 / 6            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Pain Chest wall                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Acute respiratory insufficiency                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Dyspnea due to Enlarged Uvula                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Exacerbation of COPD                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Pleural Effusion (Left)                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Pulmonary Xanthofibroma                         |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Respiratory Failure                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Endometriosis                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Injury, poisoning and procedural complications  |                  |                  |                  |
| Death (cause unknown)                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 1 / 3            |
| Death (mixed drug intoxication)                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 1 / 3            | 0 / 0            | 0 / 3            |
| Dural leak after lumbar fusion surgery          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Post-operative hematoma after oophorectomy      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Cardiac disorders                               |                  |                  |                  |
| Anemia post surgery                             |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                                 | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all             | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all                  | 0 / 3            | 0 / 0            | 0 / 3            |
| AV-Block Grade III  |                  |                  |                  |
| subjects affected / exposed                                 | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all             | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all                  | 0 / 3            | 0 / 0            | 0 / 3            |
| Palpitations  |                  |                  |                  |
| subjects affected / exposed                                 | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                  | 0 / 3            | 0 / 0            | 0 / 3            |
| Prolonged QT and sinus bradycardia                          |                  |                  |                  |
| subjects affected / exposed                                 | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all             | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all                  | 0 / 3            | 0 / 0            | 0 / 3            |
| Sinus Carotis Syndrome requiring pacemaker implantation     |                  |                  |                  |
| subjects affected / exposed                                 | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all             | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all                  | 0 / 3            | 0 / 0            | 0 / 3            |
| Cardiac Failure   |                  |                  |                  |
| subjects affected / exposed                                 | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all             | 0 / 1            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all                  | 1 / 3            | 0 / 0            | 0 / 3            |
| Cardiac ischemia  |                  |                  |                  |
| subjects affected / exposed                                 | 1 / 1007 (0.10%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all                  | 0 / 3            | 0 / 0            | 0 / 3            |
| Congestive Heart Failure                                    |                  |                  |                  |
| subjects affected / exposed                                 | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all             | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all                  | 0 / 3            | 0 / 0            | 0 / 3            |
| Dilated cardiomyopathy in context of congenital abnormality |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Hypertension                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 2 / 1007 (0.20%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Left ventricular systolic dysfunction           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Myocardial Infarction                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Severe Mitral Insufficiency                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Nervous system disorders                        |                  |                  |                  |
| Anxiety   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Carpal Tunnel Syndrome                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 3 / 1001 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 3 / 3            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Cerebrovascular Accident                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 2            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Cerebrovascular Ischemia                        |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| CNS Cerebrovascular ischemia                    |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1007 (0.30%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Concussion cerebri                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Depression                                      |                  |                  |                  |
| subjects affected / exposed                     | 5 / 1007 (0.50%) | 5 / 1007 (0.50%) | 3 / 1001 (0.30%) |
| occurrences causally related to treatment / all | 3 / 6            | 3 / 5            | 2 / 3            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Dizziness                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 3 / 1001 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 2 / 3            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Hot flushes leading to syncope                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Multiple Sclerosis                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 1 / 3            | 0 / 0            | 0 / 3            |
| Neuromyelitis optica                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Neuropathy: sensory                             |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Partial Amnesia                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Personality/Behavioral                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Suicide attempt                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Syncope   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 1 / 2            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Trigeminal neuralgia                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Vestibular neuropathy                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Eye disorders                                   |                  |                  |                  |
| Cataract and Retinal Detachment (R Eye)         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Intermittent blurred vision L eye               |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Papilledema bilateral                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Retinal Detachment                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Gastrointestinal disorders                      |                  |                  |                  |
| Abdominal Pain                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Acute Appendicitis                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Anal Fissure                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Colitis   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Dehydration due to vomiting and diarrhea        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Gastrointestinal Obstruction (small bowel)      |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Inguinal Hernia                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Pyloric Ulcer                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Gastric ulcer                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Gastrointestinal Bleeding                       |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1007 (0.20%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Pain Abdomen NOS                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Gastroenteritis                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Ischemic Colitis                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Hepatobiliary disorders                         |                  |                  |                  |
| Cholecystitis                                   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 1007 (0.20%) | 4 / 1007 (0.40%) | 4 / 1001 (0.40%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 1 / 3            |
| Cholecystolithiasis                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Cholecystolithiasis requiring surgery           |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1007 (0.30%) | 1 / 1007 (0.10%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Choledocholithiasis                             |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1007 (0.20%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Cholelithiasis                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Hepatic Adenoma                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Hepatic steatosis                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Liver dysfunction (ethylic hepatitis)           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 1 / 3            |
| Pancreatitis                                    |                  |                  |                  |

|   |                  |                   |                  |
|---|------------------|-------------------|------------------|
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%)  | 4 / 1001 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0             | 0 / 3            |
| Cellulitis                                      |                  |                   |                  |
| subjects affected / exposed                     | 4 / 1007 (0.40%) | 10 / 1007 (0.99%) | 7 / 1001 (0.70%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 11            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0             | 0 / 3            |
| Skin and subcutaneous tissue disorders          |                  |                   |                  |
| Acute generalized pustular dermatosis           |                  |                   |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%)  | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0             | 0 / 3            |
| Rash pustular                                   |                  |                   |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%)  | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0             | 0 / 3            |
| Renal and urinary disorders                     |                  |                   |                  |
| Hydronephrosis                                  |                  |                   |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%)  | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0             | 0 / 3            |
| Nephrolithiasis                                 |                  |                   |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%)  | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0             | 0 / 3            |
| Renal failure                                   |                  |                   |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%)  | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0             | 0 / 3            |
| Ureteral Obstruction                            |                  |                   |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%)  | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0             | 0 / 3            |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Ureteral stenosis (L)                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Urinary Incontinence                            |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1007 (0.20%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Endocrine disorders                             |                  |                  |                  |
| Bilateral hyperplasia of adrenal glands         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Diabetes mellitus Type 1                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Diabetes mellitus type 2                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Follicular hyperplasia of thyroid gland         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Hyperparathyroidism                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Pheochromocytoma                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| Schwannoma L benign requiring parotidectomy     |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%)  | 0 / 1001 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             | 0 / 3             |
| Struma nodosa                                   |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%)  | 0 / 1001 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             | 0 / 3             |
| Thyroid Nodule (R Thyroid)                      |                   |                   |                   |
| subjects affected / exposed                     | 1 / 1007 (0.10%)  | 0 / 1007 (0.00%)  | 0 / 1001 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             | 0 / 3             |
| Musculoskeletal and connective tissue disorders |                   |                   |                   |
| Arthritis                                       |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1007 (0.00%)  | 0 / 1007 (0.00%)  | 2 / 1001 (0.20%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 1 / 2             |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             | 0 / 3             |
| Bone Fracture                                   |                   |                   |                   |
| subjects affected / exposed                     | 16 / 1007 (1.59%) | 10 / 1007 (0.99%) | 24 / 1001 (2.40%) |
| occurrences causally related to treatment / all | 2 / 16            | 4 / 10            | 20 / 28           |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             | 0 / 3             |
| Diaphragmatic lesions (benign)                  |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%)  | 0 / 1001 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             | 0 / 3             |
| Discus Hernia                                   |                   |                   |                   |
| subjects affected / exposed                     | 1 / 1007 (0.10%)  | 1 / 1007 (0.10%)  | 1 / 1001 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             | 0 / 3             |
| Dislocation of hip prosthesis R                 |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1007 (0.00%)  | 1 / 1007 (0.10%)  | 0 / 1001 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             | 0 / 3             |



|  |                  |                  |                  |
|--|------------------|------------------|------------------|
| Meniscus Lesion  |                  |                  |                  |
| subjects affected / exposed                              | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all               | 0 / 3            | 0 / 0            | 0 / 3            |
| Osteoarthritis   |                  |                  |                  |
| subjects affected / exposed                              | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all               | 0 / 3            | 0 / 0            | 0 / 3            |
| Rheumatoid arthritis leading to R knee replacement       |                  |                  |                  |
| subjects affected / exposed                              | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all               | 0 / 3            | 0 / 0            | 0 / 3            |
| Spondylolisthesis requiring surgery (lumbal fusion L4-5) |                  |                  |                  |
| subjects affected / exposed                              | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all               | 0 / 3            | 0 / 0            | 0 / 3            |
| Wound dehiscence   |                  |                  |                  |
| subjects affected / exposed                              | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all               | 0 / 3            | 0 / 0            | 0 / 3            |
| Back pain  |                  |                  |                  |
| subjects affected / exposed                              | 2 / 1007 (0.20%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all          | 1 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all               | 0 / 3            | 0 / 0            | 0 / 3            |
| Joint pain   |                  |                  |                  |
| subjects affected / exposed                              | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 0            | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all               | 0 / 3            | 0 / 0            | 0 / 3            |
| Polytrauma   |                  |                  |                  |
| subjects affected / exposed                              | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all               | 0 / 3            | 0 / 0            | 0 / 3            |
| Infections and infestations                              |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Appendicitis                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Breast implant infection                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 1 / 1007 (0.10%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Breast Infection                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Bursitis and cellulitis (L Elbow)               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Chest Wall Infection                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| CMV Colitis, UTI and Pneumonia                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Colitis and Urinary Infection                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Erysipelas (R Arm)                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 2 / 1007 (0.20%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Infected ingrown toe nail                       |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                           | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all            | 0 / 3            | 0 / 0            | 0 / 3            |
| Infection (MRSA)                                      |                  |                  |                  |
| subjects affected / exposed                           | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all       | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all            | 0 / 3            | 0 / 0            | 0 / 3            |
| Infective endocarditis after mitral valve replacement |                  |                  |                  |
| subjects affected / exposed                           | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all            | 0 / 3            | 0 / 0            | 0 / 3            |
| Influenza A   |                  |                  |                  |
| subjects affected / exposed                           | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all            | 0 / 3            | 0 / 0            | 0 / 3            |
| L breast abscess                                      |                  |                  |                  |
| subjects affected / exposed                           | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all       | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all            | 0 / 3            | 0 / 0            | 0 / 3            |
| Meningitis  |                  |                  |                  |
| subjects affected / exposed                           | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all       | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all            | 0 / 3            | 0 / 0            | 0 / 3            |
| Peri-rectal abscess                                   |                  |                  |                  |
| subjects affected / exposed                           | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all            | 0 / 3            | 0 / 0            | 0 / 3            |
| Pneumonia   |                  |                  |                  |
| subjects affected / exposed                           | 2 / 1007 (0.20%) | 4 / 1007 (0.40%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all       | 0 / 2            | 0 / 8            | 0 / 1            |
| deaths causally related to treatment / all            | 0 / 3            | 0 / 0            | 0 / 3            |
| Pneumonia/Pleuritis                                   |                  |                  |                  |

|  |                  |                  |                  |
|--|------------------|------------------|------------------|
| subjects affected / exposed                        | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all         | 0 / 3            | 0 / 0            | 0 / 3            |
| Postoperative infection                            |                  |                  |                  |
| subjects affected / exposed                        | 0 / 1007 (0.00%) | 3 / 1007 (0.30%) | 4 / 1001 (0.40%) |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 3            | 0 / 4            |
| deaths causally related to treatment / all         | 0 / 3            | 0 / 0            | 0 / 3            |
| Pyelonephritis                                     |                  |                  |                  |
| subjects affected / exposed                        | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all    | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all         | 0 / 3            | 0 / 0            | 0 / 3            |
| Recurrent urinary tract infections                 |                  |                  |                  |
| subjects affected / exposed                        | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all         | 0 / 3            | 0 / 0            | 0 / 3            |
| Sepsis   |                  |                  |                  |
| subjects affected / exposed                        | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all         | 0 / 3            | 0 / 0            | 0 / 3            |
| Septic Shock                                       |                  |                  |                  |
| subjects affected / exposed                        | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all         | 0 / 3            | 0 / 0            | 0 / 3            |
| Skin infection                                     |                  |                  |                  |
| subjects affected / exposed                        | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all         | 0 / 3            | 0 / 0            | 0 / 3            |
| Superinfection of Posttraumatic Hematoma (R Shank) |                  |                  |                  |
| subjects affected / exposed                        | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all         | 0 / 3            | 0 / 0            | 0 / 3            |
| Urinary tract infection                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Urosepsis                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Ventriculoperitoneal shunt infection            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Wound Infection                                 |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1007 (0.30%) | 2 / 1007 (0.20%) | 2 / 1001 (0.20%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Metabolism and nutrition disorders              |                  |                  |                  |
| Dyspnea and Fatigue                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Hypoglycemia                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 0 / 1007 (0.00%) | 1 / 1001 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Hypokalemia                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1007 (0.00%) | 1 / 1007 (0.10%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |
| Increased GGT Levels                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1007 (0.10%) | 0 / 1007 (0.00%) | 0 / 1001 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 3            |

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

| <b>Non-serious adverse events</b>                         | Tamoxifen              | T+OFS                  | E+OFS                  |
|---|------------------------|------------------------|------------------------|
| Total subjects affected by non-serious adverse events     |                        |                        |                        |
| subjects affected / exposed                               | 951 / 1007<br>(94.44%) | 982 / 1007<br>(97.52%) | 980 / 1001<br>(97.90%) |
| Vascular disorders  |                        |                        |                        |
| Hot flashes/flushes                                       |                        |                        |                        |
| subjects affected / exposed                               | 727 / 1007<br>(72.19%) | 806 / 1007<br>(80.04%) | 820 / 1001<br>(81.92%) |
| occurrences (all)   | 727                    | 806                    | 820                    |
| Hypertension  |                        |                        |                        |
| subjects affected / exposed                               | 119 / 1007<br>(11.82%) | 158 / 1007<br>(15.69%) | 165 / 1001<br>(16.48%) |
| occurrences (all)   | 119                    | 158                    | 165                    |
| General disorders and administration site conditions      |                        |                        |                        |
| Fatigue (asthenia, lethargy, malaise)                     |                        |                        |                        |
| subjects affected / exposed                               | 571 / 1007<br>(56.70%) | 595 / 1007<br>(59.09%) | 591 / 1001<br>(59.04%) |
| occurrences (all)   | 571                    | 595                    | 591                    |
| Injection site reaction/extravasation changes             |                        |                        |                        |
| subjects affected / exposed                               | 4 / 1007 (0.40%)       | 88 / 1007 (8.74%)      | 84 / 1001 (8.39%)      |
| occurrences (all)   | 4                      | 88                     | 84                     |
| Immune system disorders                                   |                        |                        |                        |
| Allergic reaction/hypersensitivity (including drug fever) |                        |                        |                        |
| subjects affected / exposed                               | 31 / 1007 (3.08%)      | 42 / 1007 (4.17%)      | 46 / 1001 (4.60%)      |
| occurrences (all)   | 31                     | 42                     | 46                     |
| Reproductive system and breast disorders                  |                        |                        |                        |
| Pain - Vagina   |                        |                        |                        |
| subjects affected / exposed                               | 224 / 1007<br>(22.24%) | 240 / 1007<br>(23.83%) | 290 / 1001<br>(28.97%) |
| occurrences (all)   | 224                    | 240                    | 290                    |
| Vaginal dryness   |                        |                        |                        |
| subjects affected / exposed                               | 421 / 1007<br>(41.81%) | 500 / 1007<br>(49.65%) | 541 / 1001<br>(54.05%) |
| occurrences (all)   | 421                    | 500                    | 541                    |
| Psychiatric disorders                                     |                        |                        |                        |
| Insomnia  |                        |                        |                        |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed                    | 437 / 1007<br>(43.40%) | 529 / 1007<br>(52.53%) | 549 / 1001<br>(54.85%) |
| occurrences (all)                              | 437                    | 529                    | 549                    |
| Libido   |                        |                        |                        |
| subjects affected / exposed                    | 427 / 1007<br>(42.40%) | 477 / 1007<br>(47.37%) | 492 / 1001<br>(49.15%) |
| occurrences (all)                              | 427                    | 477                    | 492                    |
| Mood alteration - depression                   |                        |                        |                        |
| subjects affected / exposed                    | 431 / 1007<br>(42.80%) | 478 / 1007<br>(47.47%) | 476 / 1001<br>(47.55%) |
| occurrences (all)                              | 431                    | 478                    | 476                    |
| Injury, poisoning and procedural complications |                        |                        |                        |
| Fracture                                       |                        |                        |                        |
| subjects affected / exposed                    | 41 / 1007 (4.07%)      | 46 / 1007 (4.57%)      | 51 / 1001 (5.09%)      |
| occurrences (all)                              | 41                     | 46                     | 51                     |
| Thrombosis/embolism (vascular access-related)  |                        |                        |                        |
| subjects affected / exposed                    | 5 / 1007 (0.50%)       | 3 / 1007 (0.30%)       | 2 / 1001 (0.20%)       |
| occurrences (all)                              | 5                      | 3                      | 2                      |
| Cardiac disorders                              |                        |                        |                        |
| Cardiac-ischemia/infarction                    |                        |                        |                        |
| subjects affected / exposed                    | 1 / 1007 (0.10%)       | 2 / 1007 (0.20%)       | 5 / 1001 (0.50%)       |
| occurrences (all)                              | 1                      | 2                      | 5                      |
| Nervous system disorders                       |                        |                        |                        |
| Hemorrhage, CNS                                |                        |                        |                        |
| subjects affected / exposed                    | 14 / 1007 (1.39%)      | 9 / 1007 (0.89%)       | 8 / 1001 (0.80%)       |
| occurrences (all)                              | 14                     | 9                      | 8                      |
| CNS cerebrovascular ischemia                   |                        |                        |                        |
| subjects affected / exposed                    | 2 / 1007 (0.20%)       | 1 / 1007 (0.10%)       | 0 / 1001 (0.00%)       |
| occurrences (all)                              | 2                      | 1                      | 0                      |
| Gastrointestinal disorders                     |                        |                        |                        |
| Nausea   |                        |                        |                        |
| subjects affected / exposed                    | 239 / 1007<br>(23.73%) | 215 / 1007<br>(21.35%) | 228 / 1001<br>(22.78%) |
| occurrences (all)                              | 239                    | 215                    | 228                    |
| Skin and subcutaneous tissue disorders         |                        |                        |                        |
| Sweating (diaphoresis)                         |                        |                        |                        |
| subjects affected / exposed                    | 486 / 1007<br>(48.26%) | 621 / 1007<br>(61.67%) | 566 / 1001<br>(56.54%) |
| occurrences (all)                              | 486                    | 621                    | 566                    |
| Renal and urinary disorders                    |                        |                        |                        |

|  |  |  |  |
|--|--|--|--|
| Incontinence, urinary<br>subjects affected / exposed<br>occurrences (all)  | 156 / 1007<br>(15.49%)<br>156                              | 180 / 1007<br>(17.87%)<br>180                              | 120 / 1001<br>(11.99%)<br>120                              |
| Musculoskeletal and connective tissue disorders<br>Osteoporosis<br>subjects affected / exposed<br>occurrences (all)  | 123 / 1007<br>(12.21%)<br>123                              | 198 / 1007<br>(19.66%)<br>198                              | 316 / 1001<br>(31.57%)<br>316                              |
| Pain - Joint<br>subjects affected / exposed<br>occurrences (all)   | 631 / 1007<br>(62.66%)<br>631                              | 700 / 1007<br>(69.51%)<br>700                              | 778 / 1001<br>(77.72%)<br>778                              |
| Metabolism and nutrition disorders<br>Glucose, serum-high<br>(hyperglycemia)<br>subjects affected / exposed<br>occurrences (all)<br><br>Pancreatic endocrine: glucose<br>intolerance<br>subjects affected / exposed<br>occurrences (all) | 15 / 1007 (1.49%)<br>15<br><br><br>15 / 1007 (1.49%)<br>15 | 37 / 1007 (3.67%)<br>37<br><br><br>21 / 1007 (2.09%)<br>21 | 17 / 1001 (1.70%)<br>17<br><br><br>28 / 1001 (2.80%)<br>28 |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 07 October 2005 | <ol style="list-style-type: none"><li>1.Modifiedthe eligibility and other sections to include patients with bilateral breast cancer.</li><li>2.Increasedthe eligibility timeframe after chemotherapy from 6 months to 8 months.</li><li>3.Modified/clarifiedeligibility requirements including:a. Defining a premenopausal group that does not require estradiol testing;b. Clarifying definitions of surgical margins;c. Defining eligible prior malignancies.</li><li>4.Clarifiedtiming of randomization with respect to surgery, radiotherapy, and chemotherapy.</li><li>5.Clarifiedthat trastuzumab is allowed prior to and/or concurrent with protocol treatment.</li><li>6.Includednew findings about exemestane efficacy and side effects in postmenopausal women.</li><li>7.Addeddetails of treatment administration.</li><li>8.Clarifiedpathology requirements and central review.</li><li>9.Administrative corrections and updates.</li></ol>   |
| 24 August 2011  | <ol style="list-style-type: none"><li>1. Modifiedthe statistical analysis plan to compare:<ol style="list-style-type: none"><li>a. OFS + tamoxifen versus tamoxifen alone for a primary analysis with a data cut-off anticipated for the third quarterof 2013 at a median follow-up of at least 5 years.</li><li>b. OFS + exemestane versus OFS + tamoxifen in the originally-planned combined analysis of SOFT and TEXT with a data cut-off anticipated for the fall of 2013 at a median follow-up of approximately 5 years in the SOFT population.</li></ol></li><li>2. Includedbreast cancer-free interval (BCFI) and distant recurrence-free interval (DRFI) assecondary endpoints replacing systemic disease-free survival.</li><li>3. Added targeted adverse event information on diabetes and collection of anti-diabetic concomitant medications. Increased risk of diabetes has been suggested by epidemiologicstudies in men being treated with GnRH agonists for prostate cancer. Glucose intolerance (diabetes) and hyperglycemia wereadded to the case report forms as targetedadverse events.</li></ol> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported