

**Sponsor**

Novartis Pharmaceuticals

**Generic Drug Name**

Letrozole

**Trial Indication(s)**

Postmenopausal women with hormone receptor and node positive breast cancer

**Protocol Number**

CFEM345D2411

**Protocol Title**

Comparison trial of letrozole to anastrozole in the adjuvant treatment of postmenopausal women with hormone receptor and node positive breast cancer

**Clinical Trial Phase**

Phase 3

**Phase of Drug Development**

Phase 4

**Study Start/End Dates**

Study Start Date: December 2005 (Actual)

Study Completion Date: September 2014 (Actual)

**Reason for Termination (If applicable)**

Not applicable

**Study Design/Methodology**

This was a Phase IIIb open-label, randomized, multicenter study designed to evaluate the use of letrozole vs anastrozole in the adjuvant treatment of hormone receptor and lymph node positive breast cancer in postmenopausal women. Hormone receptor positive patient definition encompassed the two categories of endocrine responsive and endocrine response uncertain tumor according to the 2005 St Gallen Guidelines: only patients whose tumors had no detectable estrogen or progesterone receptor expression were considered hormone receptor negative. Pathologic assessment of axillary lymph nodes were conducted by either performing sentinel node biopsy (SNB), when appropriate (eg, in clinically negative axillary nodes), followed by axillary lymph node dissection (ALND) or by performing directly ALND (eg, in clinically positive lymph nodes). The number of lymph nodes provided for pathologic evaluation to accurately stage the axillary with the level I and level II dissection were defined according to local institutional standard practice.

**Centers**

292 centers in 21 countries: United States(47), Sweden(4), Norway(1), Netherlands(5), Korea, Republic of(3), Japan(20), Italy(20), Israel(4), Ireland(12), United Kingdom(21), France(17), Finland(1), Spain(10), Denmark(10), Germany(36), China(4), Switzerland(5), Canada(9), Belgium(17), Austria(16), Australia(30)

**Objectives:**

The objective of this study was to test whether letrozole had superior efficacy compared to anastrozole when used for the adjuvant treatment of post-menopausal women with hormone receptor and lymph node positive breast cancer.

The primary objective was to compare the rate of disease-free survival (DFS) when 959 DFS events had occurred in postmenopausal women with hormone receptor and lymph node positive breast cancer randomized between letrozole and anastrozole.

The secondary objectives were:

- To compare the general safety between the two treatment arms

- To compare the two treatment arms in a descriptive manner with the other indicators of efficacy including overall survival, time to development of distant metastases, time to development of contra lateral breast cancer and distant DFS
- Compare the effect of treatment on serum lipid profiles between treatment arms, and describe the incidence of cardiovascular events in each treatment arm
- Describe the incidence of bone fractures in each treatment arm

### **Test Product (s), Dose(s), and Mode(s) of Administration**

#### **Letrozole**

Letrozole 2.5 mg oral tablets.

#### **Anastrozole**

Anastrozole 1 mg oral tablets.

### **Statistical Methods**

Statistical hypothesis, model, and method of analysis: To test treatment difference in DFS, a stratified two-sided log-rank test was used as the primary analysis, stratifying for number of lymph nodes (1-3 or 4+) and HER2 status (positive or negative). Any patient enrolled with unknown HER2 status (the inclusion of whom was actually prohibited by the protocol) was combined with the HER2 negative category (by far the most common category).

Time to DFS event was summarized by treatment arm. Time to DFS event was analyzed by means of Kaplan-Meier method. The number of patients with DFS event and censored and the median time with 95% confidence interval (CI) was presented by treatment arm. The Kaplan-Meier-estimated event-free proportion (and 95% confidence interval) was tabulated for each treatment arm at 1-year intervals. Kaplan-Meier plot of DFS estimates for each treatment arm was also presented.

The level of significance for the primary analysis on the primary efficacy variable was set by the Lan- DeMets error spending function, which depends on the actual number of events that had been employed in the first and second interim analyses and the final analysis.

The primary efficacy variable was analyzed using the intent to treat (ITT) set.

Secondary efficacy variables and analyses: The secondary efficacy variables include overall survival, time to distant metastases, distant disease-free survival, and time to contralateral breast cancer.

Time to event was analyzed by means of Kaplan-Meier method. The number of patients with event and censored and the median time with 95% CI were presented by treatment arm.

The Kaplan-Meier-estimated event-free proportion (and 95% confidence interval) was tabulated for each treatment arm at 1-year intervals. Kaplan-Meier plot of estimates for each treatment group were also presented.

Time to event was analyzed using a Cox proportional hazard model stratified for number of lymph nodes [1-3 or 4+] and HER2 status [positive or negative]. The estimated hazard ratio (between the two treatments), its 95% confidence interval, and the corresponding p-value were displayed.

**Safety:** The assessment of safety was based mainly on the frequency of adverse events (AEs) and on the number of laboratory values that fell outside of pre-determined normal ranges.

The safety summary tables presented in the CSR include on-treatment events/assessments collected up to 28 days since the date of last study treatment administration and death during the study. All safety data were listed and those collected after 28 days from treatment discontinuation date were lagged.

### **Study Population: Key Inclusion/Exclusion Criteria**

#### **Inclusion Criteria:**

- Recent primary surgery for breast cancer
- Early stage breast cancer
- Postmenopausal
- Hormone receptor positive
- Positive lymph node involvement

#### **Exclusion Criteria:**

- Metastatic disease
- Presence of contralateral breast cancer including DCIS
- Progression

Other protocol-defined inclusion/exclusion criteria may apply.

**Participant Flow Table**
**Overall Study**

	<b>Letrozole</b>	<b>Anastrozole</b>
<b>Started</b>	2078	2094
<b>Intent-to-treat (ITT)</b>	2061	2075
<b>Safety set</b>	2049	2062
<b>Completed</b>	1317	1286
<b>Not Completed</b>	761	808
Withdrawal by Subject	71	79
Protocol Violation	35	30
Lost to Follow-up	28	35
Disease progression	196	216
Death	28	47
Adverse Event	311	296
Administrative problems	22	25
Abnormal test procedure(s) result	49	61
Abnormal laboratory values	4	0

Protocol deviation	17	19
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### **Baseline Characteristics**

	Letrozole	Anastrozole	Total
<b>Number of Participants</b> [units: participants]	2061	2075	4136
<b>Age Continuous</b> (units: Years) Mean ± Standard Deviation	63.2±8.48	63.1±8.45	63.2±8.46
<b>Gender, Customized</b> <sup>[1]</sup> (units: Participants)	2061	2075	4136

[1] Female

### **Summary of Efficacy**

#### **Primary Outcome Result(s)**

##### **Disease free survival**

	Letrozole	Anastrozole
<b>Number of Participants Analyzed</b> [units: participants]	2061	2075
<b>Disease free survival</b> (units: Months) Median (95% Confidence)	NA (84.14 to NA) <sup>¶</sup>	NA (NA to NA) <sup>¶</sup>

Interval)

[1] The median was not reached and therefore, could not be calculated.

## **Secondary Outcome Result(s)**

### **Overall survival**

	<b>Letrozole</b>	<b>Anastrozole</b>
<b>Number of Participants Analyzed [units: participants]</b>	2061	2075
<b>Overall survival</b> (units: Months) Median (95% Confidence Interval)	NA (NA to NA) <sup>[1]</sup>	NA (NA to NA) <sup>[1]</sup>

[1] The median was not reached and therefore, the median could not be calculated.

### **Time to development of distant metastases**

	<b>Letrozole</b>	<b>Anastrozole</b>
<b>Number of Participants Analyzed [units: participants]</b>	2061	2075
<b>Time to development of distant metastases</b> (units: Months) Median (95% Confidence Interval)	NA (84.14 to NA) <sup>[1]</sup>	NA (NA to NA) <sup>[1]</sup>

[1] The median was not reached and therefore, the median could not be calculated.

### **Time to development of contra lateral breast cancer**

<b>Letrozole</b>	<b>Anastrozole</b>
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**Number of Participants**

<b>Analyzed [units: participants]</b>	2061	2075
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**Time to development of  
contra lateral breast  
cancer**

(units: Months) Median (95% Confidence Interval)	NA (NA to NA) <sup>¶</sup>	NA (NA to NA) <sup>¶</sup>
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[1] The median was not reached and therefore, the median could not be calculated.

**Distant disease-free survival**

	<b>Letrozole</b>	<b>Anastrozole</b>
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**Number of Participants**

<b>Analyzed [units: participants]</b>	2061	2075
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**Distant disease-free  
survival**

(units: Months) Median (95% Confidence Interval)	NA (84.14 to NA) <sup>¶</sup>	NA (NA to NA) <sup>¶</sup>
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[1] The median was not reached and therefore, the median could not be calculated.

**Change from baseline in serum lipid profiles**

	<b>Letrozole</b>	<b>Anastrozole</b>
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**Number of Participants**

<b>Analyzed [units: participants]</b>	2049	2062
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**Change from baseline in serum lipid profiles**

(units: mg/dL)  
Mean (95% Confidence Interval)

6 months	5.643 (5.584 to	5.553 (5.495 to
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	5.701)	5.611)
12 months	5.569 (5.510 to 5.629)	5.511 (5.452 to 5.570)
24 months	5.508 (5.445 to 5.572)	5.436 (5.373 to 5.499)
36 months	5.429 (5.359 to 5.500)	5.427 (5.357 to 5.497)
48 months	5.395 (5.323 to 5.468)	5.366 (5.293 to 5.438)
60 months	5.375 (5.300 to 5.451)	5.368 (5.292 to 5.443)

**Percentage of participants who experienced clinical fracture events**

	Letrozole	Anastrozole
<b>Number of Participants Analyzed [units: participants]</b>	2049	2062
<b>Percentage of participants who experienced clinical fracture events</b> (units: Percentage of participants)	9.3	8.1

**Percentage of participants who experienced cardiovascular events**

Letrozole      Anastrozole

**Number of Participants**

<b>Analyzed [units: participants]</b>	2049	2062
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**Percentage of participants who experienced cardiovascular events**

(units: Percentage of participants)

Ischemic heart disease	2.4	1.5
Cardiac failures	1.5	0.7
Cerebrovascular accidents	1.6	1.5
Thromboembolic events	1.2	1.2

**Summary of Safety**
**Safety Results**
**Serious Adverse Events by System Organ Class**

<b>Source Vocabulary for Table Default</b>	MedDRA 15.1
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<b>Assessment Type for Table Default</b>	Systematic Assessment
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	<b>Letrozole N = 2049</b>	<b>Anastrozole N = 2062</b>
<b>Total participants affected</b>	486 (23.72%)	520 (25.22%)

**Blood and lymphatic system disorders**

**Clinical Trial Results Website**

Anaemia <sup>1</sup>	4 (0.20%)	3 (0.15%)
Autoimmune haemolytic anaemia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Haemorrhagic anaemia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Lymphadenopathy <sup>1</sup>	0 (0.00%)	2 (0.10%)
Pancytopenia <sup>1</sup>	0 (0.00%)	1 (0.05%)
<b>Cardiac disorders</b>		
Acute coronary syndrome <sup>1</sup>	1 (0.05%)	1 (0.05%)
Acute myocardial infarction <sup>1</sup>	3 (0.15%)	4 (0.19%)
Adams-Stokes syndrome <sup>1</sup>	1 (0.05%)	0 (0.00%)
Angina pectoris <sup>1</sup>	8 (0.39%)	8 (0.39%)
Angina unstable <sup>1</sup>	1 (0.05%)	2 (0.10%)
Arrhythmia <sup>1</sup>	2 (0.10%)	2 (0.10%)
Atrial fibrillation <sup>1</sup>	19 (0.93%)	15 (0.73%)
Atrioventricular block complete <sup>1</sup>	1 (0.05%)	0 (0.00%)
Bradycardia <sup>1</sup>	2 (0.10%)	1 (0.05%)
Bundle branch block <sup>1</sup>	1 (0.05%)	0 (0.00%)
Cardiac arrest <sup>1</sup>	2 (0.10%)	4 (0.19%)
Cardiac disorder <sup>1</sup>	1 (0.05%)	1 (0.05%)
Cardiac failure <sup>1</sup>	9 (0.44%)	3 (0.15%)
Cardiac failure acute <sup>1</sup>	1 (0.05%)	0 (0.00%)
Cardiac failure chronic <sup>1</sup>	3 (0.15%)	0 (0.00%)
Cardiac failure congestive <sup>1</sup>	9 (0.44%)	4 (0.19%)

**Clinical Trial Results Website**

Cardiac fibrillation <sup>1</sup>	0 (0.00%)	2 (0.10%)
Cardiac tamponade <sup>1</sup>	1 (0.05%)	0 (0.00%)
Cardiac valve disease <sup>1</sup>	0 (0.00%)	1 (0.05%)
Cardiomyopathy <sup>1</sup>	2 (0.10%)	1 (0.05%)
Cardio-respiratory arrest <sup>1</sup>	1 (0.05%)	2 (0.10%)
Cardiovascular insufficiency <sup>1</sup>	1 (0.05%)	0 (0.00%)
Conduction disorder <sup>1</sup>	0 (0.00%)	1 (0.05%)
Congestive cardiomyopathy <sup>1</sup>	0 (0.00%)	1 (0.05%)
Cor pulmonale <sup>1</sup>	1 (0.05%)	0 (0.00%)
Coronary artery disease		
Coronary artery disease <sup>1</sup>	7 (0.34%)	2 (0.10%)
Coronary artery stenosis <sup>1</sup>	2 (0.10%)	0 (0.00%)
Gastrocardiac syndrome <sup>1</sup>	1 (0.05%)	0 (0.00%)
Ischaemic cardiomyopathy <sup>1</sup>	1 (0.05%)	0 (0.00%)
Left ventricular dysfunction <sup>1</sup>	1 (0.05%)	1 (0.05%)
Left ventricular failure <sup>1</sup>	0 (0.00%)	1 (0.05%)
Mitral valve disease <sup>1</sup>	1 (0.05%)	0 (0.00%)
Mitral valve incompetence <sup>1</sup>	1 (0.05%)	0 (0.00%)
Myocardial infarction <sup>1</sup>	5 (0.24%)	4 (0.19%)
Myocardial ischaemia <sup>1</sup>	2 (0.10%)	2 (0.10%)

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Palpitations <sup>1</sup>	1 (0.05%)	1 (0.05%)
Restrictive cardiomyopathy <sup>1</sup>	1 (0.05%)	0 (0.00%)
Sick sinus syndrome <sup>1</sup>	0 (0.00%)	1 (0.05%)
Stress cardiomyopathy <sup>1</sup>	2 (0.10%)	0 (0.00%)
Supraventricular tachycardia <sup>1</sup>	2 (0.10%)	0 (0.00%)
Tachyarrhythmia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Tachycardia <sup>1</sup>	3 (0.15%)	0 (0.00%)
Tricuspid valve incompetence <sup>1</sup>	1 (0.05%)	1 (0.05%)
Ventricular extrasystoles <sup>1</sup>	1 (0.05%)	0 (0.00%)
Ventricular fibrillation <sup>1</sup>	0 (0.00%)	2 (0.10%)
Ventricular tachycardia <sup>1</sup>	0 (0.00%)	1 (0.05%)
<b>Congenital, familial and genetic disorders</b>		
Atrial septal defect <sup>1</sup>	0 (0.00%)	1 (0.05%)
Syndactyly <sup>1</sup>	0 (0.00%)	1 (0.05%)
Vitello-intestinal duct remnant <sup>1</sup>	0 (0.00%)	1 (0.05%)
<b>Ear and labyrinth disorders</b>		
Hearing impaired <sup>1</sup>	0 (0.00%)	1 (0.05%)
Inner ear disorder <sup>1</sup>	1 (0.05%)	0 (0.00%)
Tinnitus <sup>1</sup>	1 (0.05%)	0 (0.00%)
Tympanic membrane perforation <sup>1</sup>	0 (0.00%)	1 (0.05%)
Vertigo <sup>1</sup>	8 (0.39%)	1 (0.05%)

Vertigo positional <sup>1</sup>	0 (0.00%)	2 (0.10%)
<b>Endocrine disorders</b>		
Autoimmune thyroiditis <sup>1</sup>	2 (0.10%)	0 (0.00%)
Goitre <sup>1</sup>	4 (0.20%)	2 (0.10%)
Hyperparathyroidism <sup>1</sup>	0 (0.00%)	3 (0.15%)
Hypothyroidism <sup>1</sup>	1 (0.05%)	0 (0.00%)
Toxic nodular goitre <sup>1</sup>	1 (0.05%)	1 (0.05%)
<b>Eye disorders</b>		
Cataract <sup>1</sup>	9 (0.44%)	2 (0.10%)
Dacryostenosis acquired <sup>1</sup>	1 (0.05%)	0 (0.00%)
Diplopia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Glaucoma <sup>1</sup>	1 (0.05%)	1 (0.05%)
Lens dislocation <sup>1</sup>	1 (0.05%)	0 (0.00%)
Macular hole <sup>1</sup>	2 (0.10%)	1 (0.05%)
Open angle glaucoma <sup>1</sup>	1 (0.05%)	0 (0.00%)
Retinal detachment <sup>1</sup>	2 (0.10%)	0 (0.00%)
Retinal vein thrombosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Vision blurred <sup>1</sup>	1 (0.05%)	0 (0.00%)
<b>Gastrointestinal disorders</b>		
Abdominal adhesions <sup>1</sup>	0 (0.00%)	2 (0.10%)
Abdominal distension <sup>1</sup>	1 (0.05%)	1 (0.05%)
Abdominal hernia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Abdominal pain <sup>1</sup>	9 (0.44%)	5 (0.24%)
Abdominal pain lower <sup>1</sup>	1 (0.05%)	3 (0.15%)

Abdominal pain upper <sup>1</sup>	6 (0.29%)	7 (0.34%)
Abdominal wall haematoma <sup>1</sup>	0 (0.00%)	1 (0.05%)
Anal sphincter atony <sup>1</sup>	1 (0.05%)	0 (0.00%)
Ascites <sup>1</sup>	0 (0.00%)	1 (0.05%)
Colitis <sup>1</sup>	1 (0.05%)	1 (0.05%)
Colitis ischaemic <sup>1</sup>	1 (0.05%)	2 (0.10%)
Colitis microscopic <sup>1</sup>	1 (0.05%)	0 (0.00%)
Colitis ulcerative <sup>1</sup>	1 (0.05%)	0 (0.00%)
Constipation <sup>1</sup>	0 (0.00%)	3 (0.15%)
Crohn's disease <sup>1</sup>	0 (0.00%)	1 (0.05%)
Diarrhoea <sup>1</sup>	8 (0.39%)	5 (0.24%)
Diverticulum <sup>1</sup>	0 (0.00%)	1 (0.05%)
Diverticulum intestinal <sup>1</sup>	2 (0.10%)	1 (0.05%)
Duodenal ulcer <sup>1</sup>	1 (0.05%)	1 (0.05%)
Duodenal ulcer haemorrhage <sup>1</sup>	0 (0.00%)	1 (0.05%)
Dyspepsia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Dysphagia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Enterocutaneous fistula <sup>1</sup>	0 (0.00%)	1 (0.05%)
Enterovesical fistula <sup>1</sup>	0 (0.00%)	2 (0.10%)
Faecal incontinence <sup>1</sup>	0 (0.00%)	1 (0.05%)
Faeces discoloured <sup>1</sup>	0 (0.00%)	1 (0.05%)
Femoral hernia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Gastric haemorrhage <sup>1</sup>	1 (0.05%)	0 (0.00%)
Gastric polyps <sup>1</sup>	1 (0.05%)	0 (0.00%)
Gastric ulcer <sup>1</sup>	0 (0.00%)	2 (0.10%)

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Gastric ulcer haemorrhage <sup>1</sup>	0 (0.00%)	1 (0.05%)
Gastric ulcer perforation <sup>1</sup>	1 (0.05%)	0 (0.00%)
Gastritis <sup>1</sup>	3 (0.15%)	5 (0.24%)
Gastritis erosive <sup>1</sup>	2 (0.10%)	0 (0.00%)
Gastrointestinal disorder <sup>1</sup>	1 (0.05%)	1 (0.05%)
Gastrointestinal haemorrhage <sup>1</sup>	0 (0.00%)	3 (0.15%)
Gastrooesophageal reflux disease <sup>1</sup>	0 (0.00%)	1 (0.05%)
Haematemesis <sup>1</sup>	0 (0.00%)	3 (0.15%)
Haematochezia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Haemorrhoids <sup>1</sup>	1 (0.05%)	1 (0.05%)
Hiatus hernia <sup>1</sup>	2 (0.10%)	0 (0.00%)
Ileus <sup>1</sup>	3 (0.15%)	3 (0.15%)
Ileus paralytic <sup>1</sup>	1 (0.05%)	0 (0.00%)
Inflammatory bowel disease <sup>1</sup>	1 (0.05%)	1 (0.05%)
Inguinal hernia <sup>1</sup>	2 (0.10%)	2 (0.10%)
Intestinal dilatation <sup>1</sup>	0 (0.00%)	1 (0.05%)
Intestinal obstruction <sup>1</sup>	3 (0.15%)	2 (0.10%)
Intestinal perforation <sup>1</sup>	1 (0.05%)	0 (0.00%)
Intestinal polyp <sup>1</sup>	0 (0.00%)	1 (0.05%)
Large intestine polyp <sup>1</sup>	7 (0.34%)	2 (0.10%)
Melaena <sup>1</sup>	1 (0.05%)	0 (0.00%)
Mouth cyst <sup>1</sup>	1 (0.05%)	0 (0.00%)



Nausea <sup>1</sup>	11 (0.54%)	6 (0.29%)
Oesophagitis <sup>1</sup>	2 (0.10%)	1 (0.05%)
Pancreatitis <sup>1</sup>	2 (0.10%)	2 (0.10%)
Pancreatitis acute <sup>1</sup>	0 (0.00%)	1 (0.05%)
Rectal haemorrhage <sup>1</sup>	2 (0.10%)	5 (0.24%)
Small intestinal obstruction <sup>1</sup>	2 (0.10%)	3 (0.15%)
Spigelian hernia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Stomatitis <sup>1</sup>	2 (0.10%)	0 (0.00%)
Subileus <sup>1</sup>	0 (0.00%)	2 (0.10%)
Tooth loss <sup>1</sup>	0 (0.00%)	1 (0.05%)
Umbilical hernia <sup>1</sup>	2 (0.10%)	1 (0.05%)
Volvulus <sup>1</sup>	0 (0.00%)	1 (0.05%)
Vomiting <sup>1</sup>	11 (0.54%)	6 (0.29%)
<b>General disorders and administration site conditions</b>		
Asthenia <sup>1</sup>	0 (0.00%)	6 (0.29%)
Cardiac death <sup>1</sup>	2 (0.10%)	0 (0.00%)
Chest discomfort <sup>1</sup>	0 (0.00%)	1 (0.05%)
Chest pain <sup>1</sup>	2 (0.10%)	1 (0.05%)
Death <sup>1</sup>	2 (0.10%)	2 (0.10%)
Device damage <sup>1</sup>	1 (0.05%)	0 (0.00%)
Device dislocation <sup>1</sup>	0 (0.00%)	2 (0.10%)
Device malfunction <sup>1</sup>	0 (0.00%)	1 (0.05%)
Disease progression <sup>1</sup>	2 (0.10%)	2 (0.10%)
Disease recurrence <sup>1</sup>	0 (0.00%)	1 (0.05%)

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Drowning <sup>1</sup>	0 (0.00%)	1 (0.05%)
Fat necrosis <sup>1</sup>	0 (0.00%)	2 (0.10%)
Fatigue <sup>1</sup>	1 (0.05%)	2 (0.10%)
Gait disturbance <sup>1</sup>	0 (0.00%)	2 (0.10%)
General physical health deterioration <sup>1</sup>	4 (0.20%)	3 (0.15%)
Impaired healing <sup>1</sup>	1 (0.05%)	1 (0.05%)
Implant site extravasation <sup>1</sup>	1 (0.05%)	0 (0.00%)
Injection site phlebitis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Malaise <sup>1</sup>	2 (0.10%)	3 (0.15%)
Multi-organ failure <sup>1</sup>	1 (0.05%)	1 (0.05%)
Non-cardiac chest pain <sup>1</sup>	3 (0.15%)	2 (0.10%)
Oedema peripheral <sup>1</sup>	0 (0.00%)	1 (0.05%)
Pain <sup>1</sup>	0 (0.00%)	2 (0.10%)
Patient-device incompatibility <sup>1</sup>	0 (0.00%)	1 (0.05%)
Pyrexia <sup>1</sup>	2 (0.10%)	8 (0.39%)
Sudden death <sup>1</sup>	0 (0.00%)	1 (0.05%)
Thrombosis in device <sup>1</sup>	1 (0.05%)	0 (0.00%)

**Hepatobiliary disorders**

Biliary colic <sup>1</sup>	0 (0.00%)	1 (0.05%)
Cholecystitis <sup>1</sup>	7 (0.34%)	5 (0.24%)
Cholecystitis acute <sup>1</sup>	2 (0.10%)	0 (0.00%)
Cholecystitis chronic <sup>1</sup>	0 (0.00%)	1 (0.05%)
Cholelithiasis <sup>1</sup>	8 (0.39%)	11 (0.53%)
Cholestasis <sup>1</sup>	0 (0.00%)	1 (0.05%)

**Clinical Trial Results Website**

Gallbladder perforation <sup>1</sup>	0 (0.00%)	1 (0.05%)
Gallbladder polyp <sup>1</sup>	1 (0.05%)	0 (0.00%)
Hepatic cirrhosis <sup>1</sup>	1 (0.05%)	1 (0.05%)
Hepatic function abnormal <sup>1</sup>	0 (0.00%)	1 (0.05%)
Hepatic steatosis <sup>1</sup>	2 (0.10%)	0 (0.00%)
Liver disorder <sup>1</sup>	0 (0.00%)	1 (0.05%)
<b>Immune system disorders</b>		
Anaphylactic shock <sup>1</sup>	1 (0.05%)	0 (0.00%)
Drug hypersensitivity <sup>1</sup>	2 (0.10%)	1 (0.05%)
Hypersensitivity <sup>1</sup>	1 (0.05%)	0 (0.00%)
Sarcoidosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
<b>Infections and infestations</b>		
Abdominal abscess <sup>1</sup>	1 (0.05%)	0 (0.00%)
Abscess <sup>1</sup>	0 (0.00%)	1 (0.05%)
Abscess limb <sup>1</sup>	1 (0.05%)	0 (0.00%)
Abscess neck <sup>1</sup>	1 (0.05%)	0 (0.00%)
Abscess soft tissue <sup>1</sup>	0 (0.00%)	1 (0.05%)
Anal abscess <sup>1</sup>	1 (0.05%)	0 (0.00%)
Appendicitis <sup>1</sup>	1 (0.05%)	5 (0.24%)
Appendicitis perforated <sup>1</sup>	1 (0.05%)	0 (0.00%)
Arthritis bacterial <sup>1</sup>	2 (0.10%)	0 (0.00%)
Arthritis infective <sup>1</sup>	0 (0.00%)	2 (0.10%)
Breast abscess <sup>1</sup>	1 (0.05%)	1 (0.05%)
Breast cellulitis <sup>1</sup>	6 (0.29%)	4 (0.19%)

**Clinical Trial Results Website**

Bronchitis <sup>1</sup>	3 (0.15%)	4 (0.19%)
Bronchopneumonia <sup>1</sup>	1 (0.05%)	2 (0.10%)
Cellulitis <sup>1</sup>	8 (0.39%)	9 (0.44%)
Clostridium difficile colitis <sup>1</sup>	3 (0.15%)	3 (0.15%)
Cystitis <sup>1</sup>	2 (0.10%)	3 (0.15%)
Device related infection <sup>1</sup>	2 (0.10%)	1 (0.05%)
Diverticulitis <sup>1</sup>	1 (0.05%)	7 (0.34%)
Encephalitis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Endocarditis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Erysipelas <sup>1</sup>	5 (0.24%)	8 (0.39%)
Escherichia sepsis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Gallbladder empyema <sup>1</sup>	0 (0.00%)	1 (0.05%)
Gangrene <sup>1</sup>	1 (0.05%)	0 (0.00%)
Gastroenteritis <sup>1</sup>	7 (0.34%)	2 (0.10%)
Gastroenteritis Escherichia coli <sup>1</sup>	1 (0.05%)	0 (0.00%)
Gastroenteritis norovirus <sup>1</sup>	1 (0.05%)	1 (0.05%)
Helicobacter infection <sup>1</sup>	1 (0.05%)	0 (0.00%)
Herpes zoster <sup>1</sup>	0 (0.00%)	2 (0.10%)
Incision site abscess <sup>1</sup>	0 (0.00%)	1 (0.05%)
Infected skin ulcer <sup>1</sup>	1 (0.05%)	0 (0.00%)
Infection <sup>1</sup>	1 (0.05%)	3 (0.15%)
Influenza <sup>1</sup>	2 (0.10%)	0 (0.00%)
Laryngitis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Lobar pneumonia <sup>1</sup>	0 (0.00%)	1 (0.05%)

**Clinical Trial Results Website**

Localised infection <sup>1</sup>	2 (0.10%)	1 (0.05%)
Lower respiratory tract infection <sup>1</sup>	2 (0.10%)	4 (0.19%)
Lymphangitis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Mastitis <sup>1</sup>	2 (0.10%)	5 (0.24%)
Meningitis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Nosocomial infection <sup>1</sup>	0 (0.00%)	1 (0.05%)
Oral candidiasis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Osteomyelitis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Otitis media <sup>1</sup>	1 (0.05%)	0 (0.00%)
Periorbital cellulitis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Peritonitis <sup>1</sup>	2 (0.10%)	2 (0.10%)
Pharyngeal abscess <sup>1</sup>	1 (0.05%)	0 (0.00%)
Pilonidal cyst <sup>1</sup>	1 (0.05%)	0 (0.00%)
Pneumonia <sup>1</sup>	16 (0.78%)	29 (1.41%)
Pneumonia klebsiella <sup>1</sup>	0 (0.00%)	1 (0.05%)
Pneumonia legionella <sup>1</sup>	0 (0.00%)	1 (0.05%)
Post procedural cellulitis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Post procedural pneumonia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Postoperative wound infection <sup>1</sup>	2 (0.10%)	2 (0.10%)
Pseudomembranous colitis <sup>1</sup>	1 (0.05%)	1 (0.05%)
Pseudomonas bronchitis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Pyelonephritis <sup>1</sup>	1 (0.05%)	2 (0.10%)

**Clinical Trial Results Website**

Pyelonephritis acute <sup>1</sup>	1 (0.05%)	0 (0.00%)
Pyometra <sup>1</sup>	1 (0.05%)	0 (0.00%)
Respiratory tract infection <sup>1</sup>	3 (0.15%)	3 (0.15%)
Sepsis <sup>1</sup>	3 (0.15%)	8 (0.39%)
Septic shock <sup>1</sup>	0 (0.00%)	1 (0.05%)
Skin infection <sup>1</sup>	1 (0.05%)	3 (0.15%)
Soft tissue infection <sup>1</sup>	0 (0.00%)	1 (0.05%)
Staphylococcal infection <sup>1</sup>	1 (0.05%)	0 (0.00%)
Staphylococcal sepsis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Upper respiratory tract infection <sup>1</sup>	0 (0.00%)	1 (0.05%)
Urinary tract infection <sup>1</sup>	7 (0.34%)	8 (0.39%)
Urosepsis <sup>1</sup>	3 (0.15%)	3 (0.15%)
Vaginal infection <sup>1</sup>	1 (0.05%)	0 (0.00%)
Vestibular neuronitis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Viral diarrhoea <sup>1</sup>	1 (0.05%)	0 (0.00%)
Viral infection <sup>1</sup>	1 (0.05%)	0 (0.00%)
Vulvitis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Wound infection <sup>1</sup>	3 (0.15%)	1 (0.05%)
<b>Injury, poisoning and procedural complications</b>		
Acetabulum fracture <sup>1</sup>	0 (0.00%)	1 (0.05%)
Alcohol poisoning <sup>1</sup>	0 (0.00%)	1 (0.05%)
Ankle fracture <sup>1</sup>	14 (0.68%)	10 (0.48%)
Arthropod bite <sup>1</sup>	0 (0.00%)	1 (0.05%)

**Clinical Trial Results Website**

Brain contusion <sup>1</sup>	0 (0.00%)	1 (0.05%)
Cervical vertebral fracture <sup>1</sup>	0 (0.00%)	1 (0.05%)
Clavicle fracture <sup>1</sup>	0 (0.00%)	2 (0.10%)
Compression fracture <sup>1</sup>	0 (0.00%)	1 (0.05%)
Concussion <sup>1</sup>	2 (0.10%)	1 (0.05%)
Contusion <sup>1</sup>	1 (0.05%)	0 (0.00%)
Dislocation of vertebra <sup>1</sup>	1 (0.05%)	0 (0.00%)
Excoriation <sup>1</sup>	0 (0.00%)	1 (0.05%)
Face injury <sup>1</sup>	0 (0.00%)	1 (0.05%)
Facial bones fracture <sup>1</sup>	1 (0.05%)	2 (0.10%)
Fall <sup>1</sup>	17 (0.83%)	13 (0.63%)
Femoral neck fracture <sup>1</sup>	3 (0.15%)	3 (0.15%)
Femur fracture <sup>1</sup>	8 (0.39%)	2 (0.10%)
Fibula fracture <sup>1</sup>	0 (0.00%)	1 (0.05%)
Foot fracture <sup>1</sup>	3 (0.15%)	2 (0.10%)
Forearm fracture <sup>1</sup>	0 (0.00%)	1 (0.05%)
Hand fracture <sup>1</sup>	1 (0.05%)	0 (0.00%)
Head injury <sup>1</sup>	1 (0.05%)	1 (0.05%)
Hip fracture <sup>1</sup>	5 (0.24%)	4 (0.19%)
Humerus fracture <sup>1</sup>	9 (0.44%)	6 (0.29%)
Incisional hernia <sup>1</sup>	0 (0.00%)	2 (0.10%)
Joint dislocation <sup>1</sup>	2 (0.10%)	1 (0.05%)
Joint injury <sup>1</sup>	1 (0.05%)	1 (0.05%)
Laceration <sup>1</sup>	1 (0.05%)	2 (0.10%)
Ligament rupture <sup>1</sup>	1 (0.05%)	0 (0.00%)

**Clinical Trial Results Website**

Ligament sprain <sup>1</sup>	0 (0.00%)	1 (0.05%)
Lower limb fracture <sup>1</sup>	3 (0.15%)	2 (0.10%)
Lumbar vertebral fracture <sup>1</sup>	4 (0.20%)	4 (0.19%)
Meniscus injury <sup>1</sup>	2 (0.10%)	4 (0.19%)
Multiple fractures <sup>1</sup>	3 (0.15%)	3 (0.15%)
Muscle rupture <sup>1</sup>	0 (0.00%)	1 (0.05%)
Muscle strain <sup>1</sup>	0 (0.00%)	1 (0.05%)
Overdose <sup>1</sup>	1 (0.05%)	3 (0.15%)
Patella fracture <sup>1</sup>	1 (0.05%)	1 (0.05%)
Pelvic fracture <sup>1</sup>	3 (0.15%)	0 (0.00%)
Pneumothorax traumatic <sup>1</sup>	1 (0.05%)	0 (0.00%)
Post procedural complication <sup>1</sup>	1 (0.05%)	0 (0.00%)
Post procedural haemorrhage <sup>1</sup>	0 (0.00%)	2 (0.10%)
Post procedural hypothyroidism <sup>1</sup>	1 (0.05%)	0 (0.00%)
Postoperative hernia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Postoperative wound complication <sup>1</sup>	0 (0.00%)	1 (0.05%)
Procedural pain <sup>1</sup>	2 (0.10%)	0 (0.00%)
Pubis fracture <sup>1</sup>	0 (0.00%)	2 (0.10%)
Pulmonary contusion <sup>1</sup>	0 (0.00%)	1 (0.05%)
Radiation pericarditis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Radiation pneumonitis <sup>1</sup>	0 (0.00%)	2 (0.10%)
Radiation skin injury <sup>1</sup>	0 (0.00%)	2 (0.10%)



**Clinical Trial Results Website**

Radius fracture <sup>1</sup>	2 (0.10%)	7 (0.34%)
Rib fracture <sup>1</sup>	3 (0.15%)	1 (0.05%)
Road traffic accident <sup>1</sup>	0 (0.00%)	1 (0.05%)
Seroma <sup>1</sup>	0 (0.00%)	4 (0.19%)
Skull fracture <sup>1</sup>	1 (0.05%)	1 (0.05%)
Soft tissue injury <sup>1</sup>	0 (0.00%)	1 (0.05%)
Spinal compression fracture <sup>1</sup>	6 (0.29%)	2 (0.10%)
Spinal fracture <sup>1</sup>	1 (0.05%)	1 (0.05%)
Splenic rupture <sup>1</sup>	0 (0.00%)	1 (0.05%)
Sternal fracture <sup>1</sup>	1 (0.05%)	0 (0.00%)
Subdural haematoma <sup>1</sup>	3 (0.15%)	2 (0.10%)
Subdural haemorrhage <sup>1</sup>	1 (0.05%)	0 (0.00%)
Tendon rupture <sup>1</sup>	0 (0.00%)	1 (0.05%)
Thermal burn <sup>1</sup>	1 (0.05%)	0 (0.00%)
Thoracic vertebral fracture <sup>1</sup>	0 (0.00%)	1 (0.05%)
Tibia fracture <sup>1</sup>	2 (0.10%)	1 (0.05%)
Toxicity to various agents <sup>1</sup>	3 (0.15%)	0 (0.00%)
Tracheal injury <sup>1</sup>	1 (0.05%)	0 (0.00%)
Ulna fracture <sup>1</sup>	1 (0.05%)	1 (0.05%)
Upper limb fracture <sup>1</sup>	3 (0.15%)	5 (0.24%)
Vascular pseudoaneurysm <sup>1</sup>	0 (0.00%)	2 (0.10%)
Wrist fracture <sup>1</sup>	6 (0.29%)	3 (0.15%)

**Investigations**

**Clinical Trial Results Website**

Amylase increased <sup>1</sup>	0 (0.00%)	1 (0.05%)
Aspiration pleural cavity <sup>1</sup>	1 (0.05%)	0 (0.00%)
Biopsy breast <sup>1</sup>	0 (0.00%)	2 (0.10%)
Biopsy lymph gland <sup>1</sup>	1 (0.05%)	0 (0.00%)
Bone density decreased <sup>1</sup>	1 (0.05%)	0 (0.00%)
Carbohydrate antigen 15-3 increased <sup>1</sup>	0 (0.00%)	1 (0.05%)
Clostridium test positive <sup>1</sup>	1 (0.05%)	0 (0.00%)
Fibrin D dimer increased <sup>1</sup>	1 (0.05%)	0 (0.00%)
Haemoglobin decreased <sup>1</sup>	0 (0.00%)	1 (0.05%)
International normalised ratio increased <sup>1</sup>	2 (0.10%)	1 (0.05%)
Lipase increased <sup>1</sup>	0 (0.00%)	1 (0.05%)
Mammogram abnormal <sup>1</sup>	1 (0.05%)	0 (0.00%)
Mediastinal biopsy <sup>1</sup>	0 (0.00%)	1 (0.05%)
Weight decreased <sup>1</sup>	2 (0.10%)	0 (0.00%)
Weight increased <sup>1</sup>	1 (0.05%)	0 (0.00%)
<b>Metabolism and nutrition disorders</b>		
Decreased appetite <sup>1</sup>	0 (0.00%)	1 (0.05%)
Dehydration <sup>1</sup>	7 (0.34%)	1 (0.05%)
Diabetes mellitus <sup>1</sup>	2 (0.10%)	0 (0.00%)
Fluid overload <sup>1</sup>	0 (0.00%)	1 (0.05%)
Hypercalcaemia <sup>1</sup>	4 (0.20%)	2 (0.10%)
Hyperglycaemia <sup>1</sup>	2 (0.10%)	0 (0.00%)

Hypokalaemia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Hyponatraemia <sup>1</sup>	4 (0.20%)	0 (0.00%)
Hypophagia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Hypovolaemia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Obesity <sup>1</sup>	1 (0.05%)	0 (0.00%)
Type 2 diabetes mellitus <sup>1</sup>	0 (0.00%)	1 (0.05%)
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia <sup>1</sup>	9 (0.44%)	6 (0.29%)
Arthritis <sup>1</sup>	0 (0.00%)	9 (0.44%)
Back pain <sup>1</sup>	6 (0.29%)	10 (0.48%)
Bone pain <sup>1</sup>	0 (0.00%)	2 (0.10%)
Compartment syndrome <sup>1</sup>	0 (0.00%)	1 (0.05%)
Costochondritis <sup>1</sup>	1 (0.05%)	1 (0.05%)
Foot deformity <sup>1</sup>	1 (0.05%)	2 (0.10%)
Intervertebral disc protrusion <sup>1</sup>	1 (0.05%)	6 (0.29%)
Joint instability <sup>1</sup>	1 (0.05%)	0 (0.00%)
Joint stiffness <sup>1</sup>	1 (0.05%)	0 (0.00%)
Kyphosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Loose body in joint <sup>1</sup>	1 (0.05%)	0 (0.00%)
Lumbar spinal stenosis <sup>1</sup>	1 (0.05%)	1 (0.05%)
Muscle atrophy <sup>1</sup>	1 (0.05%)	0 (0.00%)
Muscle spasms <sup>1</sup>	1 (0.05%)	0 (0.00%)
Muscular weakness <sup>1</sup>	1 (0.05%)	1 (0.05%)

**Clinical Trial Results Website**

Musculoskeletal chest pain <sup>1</sup>	3 (0.15%)	4 (0.19%)
Musculoskeletal pain <sup>1</sup>	2 (0.10%)	3 (0.15%)
Musculoskeletal stiffness <sup>1</sup>	0 (0.00%)	1 (0.05%)
Myalgia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Myopathy <sup>1</sup>	0 (0.00%)	1 (0.05%)
Osteoarthritis <sup>1</sup>	21 (1.02%)	15 (0.73%)
Osteonecrosis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Osteopenia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Osteoporosis <sup>1</sup>	3 (0.15%)	1 (0.05%)
Pain in extremity <sup>1</sup>	2 (0.10%)	0 (0.00%)
Polyarthritis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Pseudarthrosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Rheumatoid arthritis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Rotator cuff syndrome <sup>1</sup>	2 (0.10%)	2 (0.10%)
Spinal column stenosis <sup>1</sup>	4 (0.20%)	1 (0.05%)
Spinal osteoarthritis <sup>1</sup>	0 (0.00%)	2 (0.10%)
Spinal pain <sup>1</sup>	2 (0.10%)	0 (0.00%)
Spondylolisthesis <sup>1</sup>	2 (0.10%)	0 (0.00%)
Synovial cyst <sup>1</sup>	0 (0.00%)	1 (0.05%)
Synovitis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Tenosynovitis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Trigger finger <sup>1</sup>	2 (0.10%)	1 (0.05%)

**Neoplasms benign, malignant and unspecified (incl cysts and polyps)**

**Clinical Trial Results Website**

Adenocarcinoma of colon <sup>1</sup>	2 (0.10%)	1 (0.05%)
Adenocarcinoma of the cervix <sup>1</sup>	0 (0.00%)	1 (0.05%)
Angiomyolipoma <sup>1</sup>	1 (0.05%)	0 (0.00%)
Basal cell carcinoma <sup>1</sup>	0 (0.00%)	1 (0.05%)
B-cell lymphoma <sup>1</sup>	1 (0.05%)	0 (0.00%)
Benign laryngeal neoplasm <sup>1</sup>	0 (0.00%)	1 (0.05%)
Benign lymph node neoplasm <sup>1</sup>	0 (0.00%)	1 (0.05%)
Benign neoplasm <sup>1</sup>	1 (0.05%)	0 (0.00%)
Benign neoplasm of thyroid gland <sup>1</sup>	0 (0.00%)	3 (0.15%)
Benign salivary gland neoplasm <sup>1</sup>	1 (0.05%)	0 (0.00%)
Bladder cancer <sup>1</sup>	1 (0.05%)	0 (0.00%)
Bone cancer <sup>1</sup>	0 (0.00%)	1 (0.05%)
Brain neoplasm <sup>1</sup>	0 (0.00%)	1 (0.05%)
Breast cancer <sup>1</sup>	1 (0.05%)	1 (0.05%)
Colon cancer <sup>1</sup>	1 (0.05%)	1 (0.05%)
Colon neoplasm <sup>1</sup>	0 (0.00%)	1 (0.05%)
Diffuse large B-cell lymphoma <sup>1</sup>	0 (0.00%)	1 (0.05%)
Fibroma <sup>1</sup>	1 (0.05%)	1 (0.05%)
Fibromatosis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Gallbladder cancer <sup>1</sup>	1 (0.05%)	0 (0.00%)
Gastric cancer <sup>1</sup>	2 (0.10%)	0 (0.00%)
Gastrointestinal	0 (0.00%)	1 (0.05%)

**Clinical Trial Results Website**

carcinoma <sup>1</sup>		
Gastrointestinal tract adenoma <sup>1</sup>	1 (0.05%)	0 (0.00%)
Glioblastoma multiforme <sup>1</sup>	1 (0.05%)	0 (0.00%)
Haemangioma <sup>1</sup>	1 (0.05%)	0 (0.00%)
Hepatic cancer <sup>1</sup>	0 (0.00%)	1 (0.05%)
Lip and/or oral cavity cancer <sup>1</sup>	0 (0.00%)	1 (0.05%)
Lip neoplasm benign <sup>1</sup>	1 (0.05%)	0 (0.00%)
Lung neoplasm malignant <sup>1</sup>	1 (0.05%)	1 (0.05%)
Lymphangiosis carcinomatosa <sup>1</sup>	0 (0.00%)	1 (0.05%)
Malignant melanoma in situ <sup>1</sup>	1 (0.05%)	0 (0.00%)
Malignant neoplasm progression <sup>1</sup>	1 (0.05%)	1 (0.05%)
Malignant peritoneal neoplasm <sup>1</sup>	0 (0.00%)	1 (0.05%)
Malignant pleural effusion <sup>1</sup>	0 (0.00%)	1 (0.05%)
Meningioma <sup>1</sup>	1 (0.05%)	1 (0.05%)
Metastases to abdominal cavity <sup>1</sup>	0 (0.00%)	1 (0.05%)
Metastases to bone <sup>1</sup>	1 (0.05%)	1 (0.05%)
Metastases to central nervous system <sup>1</sup>	1 (0.05%)	0 (0.00%)
Metastases to liver <sup>1</sup>	1 (0.05%)	0 (0.00%)
Metastases to peritoneum <sup>1</sup>	1 (0.05%)	0 (0.00%)

**Clinical Trial Results Website**

Metastatic pain <sup>1</sup>	0 (0.00%)	1 (0.05%)
Neurilemmoma benign <sup>1</sup>	1 (0.05%)	0 (0.00%)
Non-small cell lung cancer <sup>1</sup>	0 (0.00%)	1 (0.05%)
Ovarian cancer <sup>1</sup>	0 (0.00%)	1 (0.05%)
Ovarian cancer stage III <sup>1</sup>	2 (0.10%)	0 (0.00%)
Ovarian fibroma <sup>1</sup>	0 (0.00%)	1 (0.05%)
Ovarian neoplasm <sup>1</sup>	1 (0.05%)	0 (0.00%)
Pancreatic carcinoma <sup>1</sup>	0 (0.00%)	2 (0.10%)
Pituitary tumour benign <sup>1</sup>	1 (0.05%)	2 (0.10%)
Pleomorphic adenoma <sup>1</sup>	0 (0.00%)	1 (0.05%)
Rectal adenoma <sup>1</sup>	0 (0.00%)	1 (0.05%)
Rectosigmoid cancer <sup>1</sup>	0 (0.00%)	1 (0.05%)
Retro-orbital neoplasm <sup>1</sup>	0 (0.00%)	1 (0.05%)
Salivary gland neoplasm <sup>1</sup>	0 (0.00%)	1 (0.05%)
Schwannoma <sup>1</sup>	0 (0.00%)	1 (0.05%)
Seborrhoeic keratosis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Signet-ring cell carcinoma <sup>1</sup>	0 (0.00%)	1 (0.05%)
Squamous cell carcinoma <sup>1</sup>	0 (0.00%)	1 (0.05%)
Squamous cell carcinoma of skin <sup>1</sup>	1 (0.05%)	4 (0.19%)
Superficial spreading melanoma stage unspecified <sup>1</sup>	0 (0.00%)	1 (0.05%)
Thyroid adenoma <sup>1</sup>	2 (0.10%)	0 (0.00%)
Thyroid neoplasm <sup>1</sup>	0 (0.00%)	1 (0.05%)

Uterine leiomyoma <sup>1</sup>	3 (0.15%)	1 (0.05%)
Waldenstrom's macroglobulinaemia <sup>1</sup>	1 (0.05%)	0 (0.00%)
<b>Nervous system disorders</b>		
Amnesia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Ataxia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Balance disorder <sup>1</sup>	1 (0.05%)	0 (0.00%)
Carotid artery stenosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Carpal tunnel syndrome <sup>1</sup>	2 (0.10%)	6 (0.29%)
Cerebral amyloid angiopathy <sup>1</sup>	1 (0.05%)	0 (0.00%)
Cerebral haemorrhage <sup>1</sup>	0 (0.00%)	1 (0.05%)
Cerebral infarction <sup>1</sup>	1 (0.05%)	6 (0.29%)
Cerebral ischaemia <sup>1</sup>	2 (0.10%)	0 (0.00%)
Cerebrovascular accident <sup>1</sup>	8 (0.39%)	5 (0.24%)
Cervicobrachial syndrome <sup>1</sup>	1 (0.05%)	0 (0.00%)
Convulsion <sup>1</sup>	0 (0.00%)	3 (0.15%)
Dementia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Dementia Alzheimer's type <sup>1</sup>	2 (0.10%)	0 (0.00%)
Dizziness <sup>1</sup>	3 (0.15%)	6 (0.29%)
Dysarthria <sup>1</sup>	1 (0.05%)	2 (0.10%)
Encephalopathy <sup>1</sup>	1 (0.05%)	1 (0.05%)
Epilepsy <sup>1</sup>	0 (0.00%)	1 (0.05%)
Facial paresis <sup>1</sup>	1 (0.05%)	0 (0.00%)



**Clinical Trial Results Website**

Haemorrhage intracranial <sup>1</sup>	2 (0.10%)	0 (0.00%)
Headache <sup>1</sup>	3 (0.15%)	4 (0.19%)
Hepatic encephalopathy <sup>1</sup>	1 (0.05%)	0 (0.00%)
Horner's syndrome <sup>1</sup>	1 (0.05%)	0 (0.00%)
Hypoaesthesia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Hypogeusia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Intracranial aneurysm <sup>1</sup>	1 (0.05%)	2 (0.10%)
Ischaemic stroke <sup>1</sup>	1 (0.05%)	0 (0.00%)
Lumbar radiculopathy <sup>1</sup>	1 (0.05%)	0 (0.00%)
Monoplegia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Multiple sclerosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Multiple sclerosis relapse <sup>1</sup>	1 (0.05%)	0 (0.00%)
Myasthenia gravis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Optic neuritis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Parkinsonism <sup>1</sup>	0 (0.00%)	1 (0.05%)
Partial seizures <sup>1</sup>	1 (0.05%)	0 (0.00%)
Petit mal epilepsy <sup>1</sup>	1 (0.05%)	0 (0.00%)
Presyncope <sup>1</sup>	2 (0.10%)	0 (0.00%)
Sciatica <sup>1</sup>	1 (0.05%)	2 (0.10%)
Sensory loss <sup>1</sup>	0 (0.00%)	1 (0.05%)
Speech disorder <sup>1</sup>	0 (0.00%)	1 (0.05%)
Spinal claudication <sup>1</sup>	1 (0.05%)	0 (0.00%)
Spinal epidural haemorrhage <sup>1</sup>	1 (0.05%)	0 (0.00%)
Subarachnoid	3 (0.15%)	4 (0.19%)

**Clinical Trial Results Website**

haemorrhage <sup>1</sup>		
Syncope <sup>1</sup>	13 (0.63%)	4 (0.19%)
Tardive dyskinesia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Transient global amnesia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Transient ischaemic attack <sup>1</sup>	8 (0.39%)	5 (0.24%)
Tremor <sup>1</sup>	1 (0.05%)	0 (0.00%)
Trigeminal neuralgia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Vertebrobasilar insufficiency <sup>1</sup>	0 (0.00%)	1 (0.05%)
VIIIth nerve paralysis <sup>1</sup>	0 (0.00%)	2 (0.10%)
<b>Psychiatric disorders</b>		
Abnormal behaviour <sup>1</sup>	0 (0.00%)	1 (0.05%)
Agitation <sup>1</sup>	0 (0.00%)	1 (0.05%)
Anxiety <sup>1</sup>	0 (0.00%)	1 (0.05%)
Completed suicide <sup>1</sup>	0 (0.00%)	1 (0.05%)
Confusional state <sup>1</sup>	2 (0.10%)	8 (0.39%)
Delirium <sup>1</sup>	1 (0.05%)	0 (0.00%)
Depressed mood <sup>1</sup>	0 (0.00%)	3 (0.15%)
Depression <sup>1</sup>	9 (0.44%)	11 (0.53%)
Drug dependence <sup>1</sup>	1 (0.05%)	0 (0.00%)
Intentional self-injury <sup>1</sup>	0 (0.00%)	1 (0.05%)
Major depression <sup>1</sup>	1 (0.05%)	1 (0.05%)
Mental disorder <sup>1</sup>	2 (0.10%)	0 (0.00%)
Mental status changes <sup>1</sup>	3 (0.15%)	2 (0.10%)
Mood disorder due to a	0 (0.00%)	1 (0.05%)

general medical condition <sup>1</sup>		
Mood swings <sup>1</sup>	1 (0.05%)	0 (0.00%)
Somatisation disorder <sup>1</sup>	0 (0.00%)	1 (0.05%)
Suicide attempt <sup>1</sup>	1 (0.05%)	1 (0.05%)
<b>Renal and urinary disorders</b>		
Calculus bladder <sup>1</sup>	1 (0.05%)	0 (0.00%)
Calculus ureteric <sup>1</sup>	0 (0.00%)	1 (0.05%)
Calculus urinary <sup>1</sup>	1 (0.05%)	1 (0.05%)
Haematuria <sup>1</sup>	0 (0.00%)	3 (0.15%)
Hydronephrosis <sup>1</sup>	1 (0.05%)	1 (0.05%)
Hypertonic bladder <sup>1</sup>	0 (0.00%)	1 (0.05%)
Nephrolithiasis <sup>1</sup>	2 (0.10%)	2 (0.10%)
Nephrotic syndrome <sup>1</sup>	0 (0.00%)	1 (0.05%)
Polyuria <sup>1</sup>	0 (0.00%)	1 (0.05%)
Renal colic <sup>1</sup>	2 (0.10%)	1 (0.05%)
Renal failure <sup>1</sup>	1 (0.05%)	7 (0.34%)
Renal failure acute <sup>1</sup>	6 (0.29%)	2 (0.10%)
Renal failure chronic <sup>1</sup>	0 (0.00%)	1 (0.05%)
Renal impairment <sup>1</sup>	1 (0.05%)	0 (0.00%)
Stress urinary incontinence <sup>1</sup>	1 (0.05%)	0 (0.00%)
Urethral caruncle <sup>1</sup>	0 (0.00%)	1 (0.05%)
Urethral obstruction <sup>1</sup>	1 (0.05%)	0 (0.00%)
Urinary incontinence <sup>1</sup>	0 (0.00%)	4 (0.19%)
Urinary tract obstruction <sup>1</sup>	0 (0.00%)	1 (0.05%)

**Reproductive system  
and breast disorders**

Adnexa uteri mass <sup>1</sup>	0 (0.00%)	1 (0.05%)
Anisomastia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Breast calcifications <sup>1</sup>	1 (0.05%)	0 (0.00%)
Breast fibrosis <sup>1</sup>	0 (0.00%)	2 (0.10%)
Breast haematoma <sup>1</sup>	1 (0.05%)	1 (0.05%)
Breast inflammation <sup>1</sup>	0 (0.00%)	2 (0.10%)
Breast mass <sup>1</sup>	1 (0.05%)	2 (0.10%)
Breast oedema <sup>1</sup>	1 (0.05%)	0 (0.00%)
Colpocele <sup>1</sup>	0 (0.00%)	1 (0.05%)
Cystocele <sup>1</sup>	1 (0.05%)	1 (0.05%)
Endometrial hyperplasia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Female genital tract fistula <sup>1</sup>	1 (0.05%)	1 (0.05%)
Genital prolapse <sup>1</sup>	1 (0.05%)	0 (0.00%)
Metrorrhagia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Nipple disorder <sup>1</sup>	0 (0.00%)	1 (0.05%)
Nipple exudate bloody <sup>1</sup>	0 (0.00%)	1 (0.05%)
Ovarian cyst <sup>1</sup>	5 (0.24%)	3 (0.15%)
Pelvic prolapse <sup>1</sup>	1 (0.05%)	0 (0.00%)
Perineal pain <sup>1</sup>	1 (0.05%)	0 (0.00%)
Rectocele <sup>1</sup>	0 (0.00%)	2 (0.10%)
Uterine fistula <sup>1</sup>	0 (0.00%)	1 (0.05%)
Uterine polyp <sup>1</sup>	2 (0.10%)	1 (0.05%)
Uterine prolapse <sup>1</sup>	2 (0.10%)	1 (0.05%)

Vaginal haemorrhage <sup>1</sup>	0 (0.00%)	2 (0.10%)
Vaginal inflammation <sup>1</sup>	1 (0.05%)	0 (0.00%)
Vaginal prolapse <sup>1</sup>	1 (0.05%)	0 (0.00%)
<b>Respiratory, thoracic and mediastinal disorders</b>		
Acute pulmonary oedema <sup>1</sup>	1 (0.05%)	0 (0.00%)
Acute respiratory failure <sup>1</sup>	0 (0.00%)	2 (0.10%)
Aspiration <sup>1</sup>	1 (0.05%)	0 (0.00%)
Asthma <sup>1</sup>	1 (0.05%)	3 (0.15%)
Bronchial hyperreactivity <sup>1</sup>	0 (0.00%)	1 (0.05%)
Bronchospasm <sup>1</sup>	1 (0.05%)	0 (0.00%)
Choking <sup>1</sup>	1 (0.05%)	0 (0.00%)
Chronic obstructive pulmonary disease <sup>1</sup>	6 (0.29%)	9 (0.44%)
Dyspnoea <sup>1</sup>	10 (0.49%)	7 (0.34%)
Dyspnoea exertional <sup>1</sup>	1 (0.05%)	0 (0.00%)
Emphysema <sup>1</sup>	1 (0.05%)	1 (0.05%)
Epistaxis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Haemoptysis <sup>1</sup>	1 (0.05%)	2 (0.10%)
Hypercapnia <sup>1</sup>	0 (0.00%)	1 (0.05%)
Hypoxia <sup>1</sup>	2 (0.10%)	1 (0.05%)
Idiopathic pulmonary fibrosis <sup>1</sup>	0 (0.00%)	2 (0.10%)
Pleural effusion <sup>1</sup>	5 (0.24%)	3 (0.15%)
Pleuritic pain <sup>1</sup>	0 (0.00%)	1 (0.05%)

**Clinical Trial Results Website**

Pneumonia aspiration <sup>1</sup>	2 (0.10%)	0 (0.00%)
Pneumothorax <sup>1</sup>	3 (0.15%)	3 (0.15%)
Productive cough <sup>1</sup>	1 (0.05%)	0 (0.00%)
Pulmonary embolism <sup>1</sup>	6 (0.29%)	12 (0.58%)
Pulmonary fibrosis <sup>1</sup>	1 (0.05%)	1 (0.05%)
Pulmonary hypertension <sup>1</sup>	2 (0.10%)	0 (0.00%)
Pulmonary oedema <sup>1</sup>	2 (0.10%)	0 (0.00%)
Respiratory distress <sup>1</sup>	1 (0.05%)	0 (0.00%)
Respiratory failure <sup>1</sup>	3 (0.15%)	3 (0.15%)
Sinus congestion <sup>1</sup>	1 (0.05%)	0 (0.00%)
Sleep apnoea syndrome <sup>1</sup>	0 (0.00%)	1 (0.05%)
<b>Skin and subcutaneous tissue disorders</b>		
Alopecia <sup>1</sup>	1 (0.05%)	0 (0.00%)
Dermal cyst <sup>1</sup>	0 (0.00%)	1 (0.05%)
Erythema multiforme <sup>1</sup>	2 (0.10%)	0 (0.00%)
Erythrodermic psoriasis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Hypertrophic scar <sup>1</sup>	0 (0.00%)	1 (0.05%)
Keloid scar <sup>1</sup>	0 (0.00%)	1 (0.05%)
Pruritus <sup>1</sup>	1 (0.05%)	0 (0.00%)
Rash maculo-papular <sup>1</sup>	1 (0.05%)	0 (0.00%)
Skin lesion <sup>1</sup>	0 (0.00%)	1 (0.05%)
Skin necrosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Urticaria <sup>1</sup>	0 (0.00%)	1 (0.05%)
Urticaria chronic <sup>1</sup>	0 (0.00%)	1 (0.05%)

**Surgical and medical procedures**

Breast lump removal <sup>1</sup>	1 (0.05%)	0 (0.00%)
Breast operation <sup>1</sup>	1 (0.05%)	0 (0.00%)
Breast prosthesis implantation <sup>1</sup>	5 (0.24%)	10 (0.48%)
Breast prosthesis removal <sup>1</sup>	1 (0.05%)	1 (0.05%)
Breast reconstruction <sup>1</sup>	24 (1.17%)	16 (0.78%)
Central venous catheter removal <sup>1</sup>	0 (0.00%)	1 (0.05%)
Knee arthroplasty <sup>1</sup>	1 (0.05%)	0 (0.00%)
Mammoplasty <sup>1</sup>	6 (0.29%)	3 (0.15%)
Mastectomy <sup>1</sup>	5 (0.24%)	6 (0.29%)
Mechanical ventilation <sup>1</sup>	0 (0.00%)	1 (0.05%)
Medical device removal <sup>1</sup>	1 (0.05%)	0 (0.00%)
Meniscus removal <sup>1</sup>	1 (0.05%)	0 (0.00%)
Modified radical mastectomy <sup>1</sup>	1 (0.05%)	0 (0.00%)
Removal of internal fixation <sup>1</sup>	1 (0.05%)	0 (0.00%)
Scar excision <sup>1</sup>	0 (0.00%)	2 (0.10%)
Spinal laminectomy <sup>1</sup>	0 (0.00%)	1 (0.05%)
Wound treatment <sup>1</sup>	1 (0.05%)	0 (0.00%)

**Vascular disorders**

Aortic aneurysm <sup>1</sup>	2 (0.10%)	1 (0.05%)
Aortic aneurysm rupture <sup>1</sup>	1 (0.05%)	0 (0.00%)

**Clinical Trial Results Website**

Aortic dissection <sup>1</sup>	2 (0.10%)	1 (0.05%)
Aortic stenosis <sup>1</sup>	2 (0.10%)	1 (0.05%)
Aortic thrombosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Arterial disorder <sup>1</sup>	1 (0.05%)	0 (0.00%)
Arterial occlusive disease <sup>1</sup>	1 (0.05%)	0 (0.00%)
Arteriosclerosis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Capillary fragility <sup>1</sup>	1 (0.05%)	0 (0.00%)
Circulatory collapse <sup>1</sup>	3 (0.15%)	4 (0.19%)
Deep vein thrombosis <sup>1</sup>	2 (0.10%)	8 (0.39%)
Embolism <sup>1</sup>	0 (0.00%)	1 (0.05%)
Extremity necrosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Femoral artery occlusion <sup>1</sup>	1 (0.05%)	0 (0.00%)
Haematoma <sup>1</sup>	2 (0.10%)	2 (0.10%)
Haemorrhage <sup>1</sup>	1 (0.05%)	0 (0.00%)
Hypertension <sup>1</sup>	7 (0.34%)	4 (0.19%)
Hypertensive crisis <sup>1</sup>	4 (0.20%)	0 (0.00%)
Hypotension <sup>1</sup>	3 (0.15%)	1 (0.05%)
Hypovolaemic shock <sup>1</sup>	0 (0.00%)	1 (0.05%)
Iliac artery occlusion <sup>1</sup>	1 (0.05%)	1 (0.05%)
Intra-abdominal haematoma <sup>1</sup>	0 (0.00%)	1 (0.05%)
Lymphocele <sup>1</sup>	0 (0.00%)	1 (0.05%)
Lymphoedema <sup>1</sup>	2 (0.10%)	3 (0.15%)
Orthostatic hypotension <sup>1</sup>	0 (0.00%)	2 (0.10%)
Peripheral arterial occlusive disease <sup>1</sup>	0 (0.00%)	1 (0.05%)



**Clinical Trial Results Website**

Peripheral artery stenosis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Peripheral ischaemia <sup>1</sup>	1 (0.05%)	1 (0.05%)
Peripheral vascular disorder <sup>1</sup>	1 (0.05%)	0 (0.00%)
Peripheral venous disease <sup>1</sup>	0 (0.00%)	1 (0.05%)
Temporal arteritis <sup>1</sup>	0 (0.00%)	1 (0.05%)
Thromboangiitis obliterans <sup>1</sup>	1 (0.05%)	0 (0.00%)
Thrombosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Varicose vein <sup>1</sup>	0 (0.00%)	2 (0.10%)
Vena cava thrombosis <sup>1</sup>	1 (0.05%)	0 (0.00%)
Venous thrombosis limb <sup>1</sup>	1 (0.05%)	0 (0.00%)

<sup>1</sup> MedDRA

**Other Adverse Events by System Organ Class**

**Source Vocabulary for Table Default** MedDRA 15.1

**Assessment Type for Table Default** Systematic Assessment

**Frequent Event Reporting Threshold** 5%

	<b>Letrozole N = 2049</b>	<b>Anastrozole N = 2062</b>
<b>Total participants affected</b>	1747 (85.26%)	1762 (85.45%)

**Blood and lymphatic**

**system disorders**

Anaemia		
<b>Gastrointestinal disorders</b>		
Nausea <sup>1</sup>	127 (6.20%)	148 (7.18%)
<b>General disorders and administration site conditions</b>		
Fatigue <sup>1</sup>	345 (16.84%)	341 (16.54%)
Oedema peripheral <sup>1</sup>	100 (4.88%)	104 (5.04%)
<b>Injury, poisoning and procedural complications</b>		
Radiation skin injury <sup>1</sup>	120 (5.86%)	88 (4.27%)
<b>Metabolism and nutrition disorders</b>		
Hypercholesterolaemia <sup>1</sup>	155 (7.56%)	151 (7.32%)
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia <sup>1</sup>	983 (47.97%)	983 (47.67%)
Back pain <sup>1</sup>	207 (10.10%)	187 (9.07%)
Bone pain <sup>1</sup>	138 (6.73%)	120 (5.82%)
Musculoskeletal pain <sup>1</sup>	122 (5.95%)	144 (6.98%)
Myalgia <sup>1</sup>	232 (11.32%)	211 (10.23%)
Osteopenia <sup>1</sup>	202 (9.86%)	172 (8.34%)
Osteoporosis <sup>1</sup>	221 (10.79%)	224 (10.86%)
Pain in extremity <sup>1</sup>	167 (8.15%)	174 (8.44%)
<b>Nervous system disorders</b>		

Dizziness <sup>1</sup>	92 (4.49%)	107 (5.19%)
Headache <sup>1</sup>	127 (6.20%)	164 (7.95%)
<b>Psychiatric disorders</b>		
Depression <sup>1</sup>	141 (6.88%)	129 (6.26%)
Insomnia <sup>1</sup>	160 (7.81%)	149 (7.23%)
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough <sup>1</sup>	106 (5.17%)	120 (5.82%)
Dyspnoea <sup>1</sup>	111 (5.42%)	92 (4.46%)
<b>Skin and subcutaneous tissue disorders</b>		
Alopecia <sup>1</sup>	126 (6.15%)	134 (6.50%)
<b>Vascular disorders</b>		
Hot flush <sup>1</sup>	666 (32.50%)	666 (32.30%)
Hypertension <sup>1</sup>	152 (7.42%)	145 (7.03%)
Lymphoedema <sup>1</sup>	158 (7.71%)	177 (8.58%)

<sup>1</sup> MedDRA

### **Conclusion:**

The study was designed to address the question as to whether letrozole would have superior efficacy compared to anastrozole for the adjuvant treatment of post-menopausal women with hormone receptor and lymph node positive breast cancer.

The study did not meet its primary objective. The primary endpoint DFS (disease free survival) was not statistically significantly different between the treatment arms (stratified Log-rank test  $p=0.3150$ , two-sided) with an estimated 7% risk reduction in the letrozole arm compared to the anastrozole arm (Hazard ratio: 0.93 with 95% CI: 0.80, 1.07).

The overall survival (OS) was not statistically significantly different between the treatment arms  $p=0.7916$  (11.4% in the letrozole arm and 11.7% in the anastrozole arm).

The TDM (time to development of distant metastases) was not statistically significantly different between the treatment arms  $p=0.9391$  (10.8% in the letrozole arm vs 10.8% in the anastrozole arm).

The DDFS (distant disease-free survival) was not statistically significantly different between the treatment arms  $p=0.6204$  (15.7% in the letrozole arm vs 16.2% in the anastrozole arm).

The median DFS, OS, TDM, and DDFS (95% CI) were not reached in either of the treatment arms. Patient exposure to the study treatments were considered to be appropriate to allow for an adequate assessment of safety. The median duration of treatment was 59.76 months for both treatment arms.

Treatment arms were well-balanced with respect to baseline demographic characteristics. The median age was 62 years in both treatment arms and approximately 86% of the patients in both treatment arms were Caucasian.

Any ongoing endocrine therapy and outcome data were not collected beyond when patients finished their 5 years of study therapy and thus this trial cannot address whether letrozole might have a beneficial impact vs anastrozole on DFS beyond 5 years.

We cannot determine the reason behind the lower than expected event rate. It may have been due in part to patients going onto another endocrine agent, other treatment options, and/or continuing endocrine therapy beyond 5 years as this data was not part of the analysis since the trial was terminated prior to the full implementation of Amendment 5 which would allow for the collection of this data.

Adverse events (AEs), SAEs (Serious Adverse Events), AEs leading to study drug discontinuation, and AEs leading to dose reduction and/or interruption of therapy were reported equally across the two treatment arms. The overall frequency of AEs was comparable between the treatment arms. There was a higher number of patients with grade 3/4 adverse events in the letrozole arm (30.6%) vs the anastrozole arm (28.7%). The most commonly affected SOCs (System Organ Class) were musculoskeletal and connective tissue disorders (75.9% vs 75.5%), vascular disorders (44.1% vs 45.1%), general disorders and administration site conditions (30.7% vs 30.9%), gastrointestinal disorders (28.8% vs 29.7%), and skin and subcutaneous tissue disorders (26.5% vs 26.5%), letrozole vs anastrozole arms, respectively.

The most common adverse events in letrozole and anastrozole arms, respectively, were arthralgia (48.2% vs 47.9%), hot flush (32.5% vs 32.3%), fatigue (16.8% vs 16.6%), osteoporosis (10.9% vs 10.9%), myalgia (11.4% vs 10.3%), and back pain (10.3% vs 9.4%). A total of 235 letrozole patients (11.5%) and 240 anastrozole patients (11.6%) died during the study. Forty-two (2.0%) letrozole patients and 46 (2.2%) anastrozole patients died up to 28 days after the end of treatment.

**Clinical Trial Results Website**

The main causes of on-treatment deaths (up to 28 days after end of treatment) on letrozole and anastrozole arms, respectively, were breast cancer (0.5% vs 0.3%), cardiac failure (0.2% vs <0.1%), and chronic obstructive pulmonary disease (0.0% vs 0.1%).

Distant recurrence occurred in 11% of both treatment arms and the sites were also equivalent across treatment arms. Secondary malignancies occurred in 4.1% and 4.8% of the letrozole and anastrozole treatment arms, respectively. Deaths occurred in 11.4% and 11.7% of the letrozole and anastrozole treatment arms, respectively.

The study size and duration were not sufficient to answer the primary and secondary objectives and found no difference between letrozole and anastrozole in safety and tolerability in the 5 year study.

**Date of Clinical Trial Report**

7-Sep-2015.