NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Lapatinib/LAP016 (GW572016)

Trial Indication(s)

Epidermal Growth Factor Receptor 2 (ErbB2) overexpressing metastatic breast cancer

Protocol Number

EGF100161 / CLAP016A2101

Protocol Title

An open-label, multicenter, Phase I/II dose escalation study of oral GW572016 in combination with docetaxel (Taxotere) plus trastuzumab (Herceptin) in subjects previously untreated for ErbB2-overexpressing metastatic breast cancer

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I/II

Study Start/End Dates

Study Start Date: September 2005 (Actual)
Primary Completion Date: June 2010 (Actual)
Study Completion Date: June 2022 (Actual)

Reason for Termination (If applicable)

EGF100161 (NCT00251433) was terminated in Phase I (Phase II expansion portion of the study was never initiated) by sponsor decision.

Study Design/Methodology

This Phase I/II dose escalation study, LAP016A2101/EGF100161, was to evaluate the tumor response rate, as well as the safety, tolerability, and efficacy of this combination in subjects with previously untreated metastatic breast cancer (MBC) whose tumors over-express Human epidermal growth factor receptor 2 (HER2)/ epidermal growth factor receptor 2 (ErbB2) receptors.

Phase I Part of Study: Subjects with previously untreated MBC with over-expression of ErbB2 were enrolled in open-label sequential cohorts of 3 or 6 subjects to determine the OTR of lapatinib, docetaxel, and trastuzumab. The OTR was defined as the dose level at which no more than one subject out of six experienced a DLT during the first treatment cycle.

The Phase I part of the study included cohorts of 3 subjects, to investigate doses of lapatinib (750mg, 1000mg, 1250mg, 1500mg) with 75mg/m2 3-weekly docetaxel plus standard weekly doses of trastuzumab with prophylactic use of growth factors.

- Following successful completion of the 1500mg lapatinib with 75mg/m2 once every 3 weeks docetaxel plus standard weekly doses of trastuzumab (Cohort 1D), additional subjects were planned to be enrolled into this cohort. This was to obtain further data with this regimen.
- Further cohorts were explored with prophylactic use of growth factors at the doses stipulated in the Phase I dose escalation schema.

Phase II Part of Study: Once the OTR of the triplet regimen was determined, the additional Cohort Y was to be included to determine safety and tolerability of once every 3 weeks trastuzumab with lapatinib and docetaxel. Following satisfactory safety data review of Cohort Y, the open-label Phase II part of the study was to begin.

In the Phase II part, subjects were to be pre-stratified for Eastern Cooperative Oncology Group (ECOG) performance (0 vs. 1) and site of disease (visceral vs. non-visceral) and subsequently randomized in a 2:1 ratio to receive either the triplet regimen or the docetaxel and trastuzumab combination.

Enrollment in the Phase I part of the study was halted on 04-Aug-2010 after 3 subjects were enrolled into the cohort dose level 5 (lapatinib 1250mg, docetaxel 100mg/m2, trastuzumab). No subjects experienced a DLT at this dose level. Thus, the OTR dose regimen of lapatinib with the higher docetaxel dose (100mg/m2) was not determined and the Phase II part of the study did not proceed.

The recruitment in the study was halted due to difficulty in recruiting subjects. This decision was not based on safety concerns arising from this study or any other lapatinib study.

Long Term Follow-up (LTFU) phase of the study: In 2012, Protocol Amendment 05 was released (28-Aug-2012), which limited the amount of data collected in the study. Based on Protocol Amendment 05, many study-specific assessments were discontinued while allowing subjects who remained on study treatment to enroll in a LTFU phase. This was done to provide continued access to this treatment for the 5 subjects who were receiving study treatment at that time, until the occurrence of unacceptable toxicity, disease progression (as determined by the Investigator), or withdrawal for any reason.

Centers

5 centers in 3 countries: France(2), Ireland(2), United States(1)

Objectives:

Objectives:

Phase I primary objectives	Endpoints
• To determine the OTR of lapatinib when administered in combination with both docetaxel and trastuzumab.	• The OTR for the triple combination will be defined as the dose level at which no more than one subject out of six experiences a dose-limiting toxicity (DLT) after completing one treatment cycle.
• To assess the safety and tolerability of lapatinib when administered in combination with both docetaxel and trastuzumab.	• Adverse events and changes from baseline in laboratory values will be evaluated to assess safety and tolerability.
Phase I secondary objectives	**Endpoints**
• To determine the clinical activity of lapatinib when administered in combination with both docetaxel and trastuzumab. • To explore any correlations between plasma concentrations of docetaxel and lapatinib and the safety data with the triplet combination. • To explore α-1-acid glycoprotein and albumin concentrations for potential correlation between drug concentration and any emerging toxicity. • To investigate doses of lapatinib (750mg, 1000mg, 1250mg, 1500mg) with 75mg/m2 once every 3 weeks docetaxel plus standard weekly doses of trastuzumab with prophylactic use of growth factors in all subjects. • To assess safety and tolerability of lapatinib when administered in combination with once every 3 weeks docetaxel and 3-weekly trastuzumab and once every 3 weeks trastuzumab with lapatinib as maintenance	• Response rate (i.e., complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD]) according to RECIST • Duration of response • Time to response • Time to progression • Overall survival (time to death)$ • PK endpoints: Cmin, Cmax • Concentrations of α-1-acid glycoprotein and albumin. • Adverse events and changes from baseline

therapy following completion of the docetaxel chemotherapy course.

$ Overall survival was not analyzed due to limited number of subjects.

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

Enrollment to the Phase I part of the study was planned to proceed with ascending doses of both lapatinib and docetaxel, but this was halted after subjects were enrolled in dose level 5 (lapatinib 1250mg, docetaxel 100mg/m 2, trastuzumab) due to reasons other than toxicity, (i.e. difficulty in recruiting subjects to the study), thus the OTR dose regimen of lapatinib with the higher docetaxel dose (100mg/m2) was not determined, and the Phase II part of the study did not proceed.

Statistical Methods

All statistical analyses were performed at the end of the study by Novartis. The safety population, which consisted of all subjects who received at least one dose of study medication (lapatinib, docetaxel or trastuzumab), was used for both safety and efficacy analyses. The analysis of the primary endpoint, i.e. determination of the OTR, was described in the primary CSR, dated 31-May-2011.

The RECIST guidelines were used to assess clinical activity and disease status. Since there was no independently reviewed confirmed response, only the Investigator responses were reported. All efficacy analyses were based on the safety population.

Overall response rate (ORR) is defined as the percentage of subjects achieving either a confirmed CR or PR. This was based on confirmed responses from the Investigator assessment of best overall response (the best response from the start of the treatment until disease progression/recurrence).

Adverse events were graded according to the NCI- Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0 and were coded to the Preferred Term (PT) level using the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Subjects must be 18 years of age.

Criteria for female subjects:
- Non-child-bearing potential (i.e., women with functioning ovaries who have a current documented tubal ligation or hysterectomy, or women who are post- menopausal);
- Child-bearing potential (i.e., women with functioning ovaries and no documented impairment of oviductal or uterine function that would cause sterility.) This category includes women with oligomenorrhoea (severe), women who are perimenopausal, and young women who have begun to menstruate. These subjects must have a negative serum pregnancy test at screening and agree to one of the following:
- Complete abstinence from intercourse from 2 weeks prior to administration of the first dose of study medication until 28 days after the final dose of study medication; or
- Consistent and correct use of one of the following acceptable methods of birth control:
- male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject; implants of levonorgestrel;
injectable progestogen;
any intrauterine device (IUD) with a documented failure rate of less than 1% per year;
oral contraceptives (either combined or progestogen only); or
barrier methods, including diaphragm or condom with a spermicide.
- Subjects must have an ECOG Performance Status of 0 to 1.
- Subjects must have histologically- or cytologically-confirmed invasive breast cancer with Stage IV disease.
- Subjects must have measurable lesion(s) according to RECIST criteria for phase II, however for phase I subjects evaluable disease will be allowed (including patients with bone lesion only disease).
- Prior to enrolment in the Phase I part of the study, subjects must have documentation of ErbB2 over-expression via IHC3+ or FISH+ testing. Prior to enrolment in the Phase II part of the study, subjects must have ErbB2 over-expression confirmed by a central laboratory,
- Subjects with stable CNS metastases or leptomeningeal involvement are eligible only if they are not taking oral steroids or enzyme-inducing anticonvulsants. Subjects with CNS only disease will not be allowed.
- Subjects that received prior radiotherapy must have completed radiotherapy treatment at least 4 weeks before enrolment and recovered from all treatment-related toxicities.
- Subjects must have new or archived tumour tissue available prior to study entry to evaluate levels of relevant biomarkers.
- Subjects must have a cardiac ejection fraction within the institutional range of normal as measured by Multigated Acquisition (MUGA) scan or echocardiogram (ECHO).
- Subjects must have adequate haematological, hepatic, and renal function.

Haemoglobin ≥9gm/dL
Absolute granulocyte count ≥1500/mm³ (1.5 x 10^9/L)
Platelets ≥75,000/mm³ (75 x 10^9/L)
Total bilirubin ≤1.5mg/dL
Both ALT and AST ≤1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase ≤2.5 times the ULN (See Taxotere Data Sheet)
Serum creatinine ≤ 2.0mg/dL or calculated creatinine clearance (CrCl) ≥40mL/min according to the formula of Cockcroft and Gault
- Subjects who received a taxane as part of adjuvant or neoadjuvant therapy are eligible if they had progression of their disease more than 6 months after completion of treatment.
- Subjects who received prior ErbB inhibitors in the adjuvant setting will be allowed, but a disease-free interval of at least 6 months must be demonstrated after the end of therapy.

Exclusion Criteria:

- Subject has peripheral neuropathy of grade 2 or higher;
- Subject has had prior systemic therapy (except one line of hormonal therapy) for metastatic disease. Also, any subjects with prior chemotherapy in the adjuvant or neoadjuvant setting with anthracycline or anthracenedione-containing regimens with cumulative doses of ≥360mg/m² of doxorubicin, ≥720mg/m² of epirubicin, or ≥72mg/m² of mitoxantrone;
- Subjects with prior systemic investigational drugs within the past 30 days or topical investigational drugs within the past 7 days;
- Subjects with uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure;
- Subjects with a known immediate or delayed hypersensitivity or untoward reaction to docetaxel, trastuzumab, or other related compounds, or to drugs chemically related to lapatinib. These include other aminoquinazolines, such as gefitinib (Iressa), erlotinib (Tarceva), or other chemically-related compounds.
- Subjects taking any prohibited medications
- Subject neither affiliated with, nor beneficiary of a social security category (For France only)

Participant Flow Table

Overall Study

	Phase I: Dose Level 0	Phase I: Dose Level 1	Phase I: Dose Level 1A	Phase I: Dose Level 1B	Phase I: Dose Level 1C	Phase I: Dose Level 1D	Phase I: Dose Level 2	Phase I: Dose Level 3	Phase I: Dose Level 4	Phase I: Dose Level 5	Total
Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Started	6	3	12	5	4	3	5	6	6	3	53
Completed	6	1	5	3	1	1	4	3	0	2	26
Not Completed	0	2	7	2	3	2	1	3	6	1	27
Adverse Event	0	0	0	0	1	0	1	1	1	0	4
Other pre-specifie	0	2	7	2	2	2	0	2	5	1	23

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Baseline Characteristics

	Phase I: Dose Level 0	Phase I: Dose Level 1	Phase I: Dose Level 1A	Phase I: Dose Level 1B	Phase I: Dose Level 1C	Phase I: Dose Level 1D	Phase I: Dose Level 2	Phase I: Dose Level 3	Phase I: Dose Level 4	Phase I: Dose Level 5	Total
Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	
Number of Participants [units:	6	3	12	5	4	3	5	6	6	3	53

participants]											
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)											
Female	6	3	12	5	4	3	5	6	6	3	53
Male	0	0	0	0	0	0	0	0	0	0	0
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)											
White	6	3	12	5	4	3	5	5	6	3	52
Asian	0	0	0	0	0	0	0	1	0	0	1
Age Continuous (units: Years) Mean ± Standard Deviation											
	45.2±11.92	49.7±7.51	46.2±9.43	54.4±12.74	44.0±10.03	53.0±7.00	50.0±10.70	53.7±8.04	55.8±10.93	43.3±11.02	49.4±10.24

Primary Outcome Result(s)

Phase I: Determination of the optimally tolerated regimen (OTR)

(Time Frame: From first initiated treatment on 19-Jan-2006 to the data cut-off date for primary CSR on 9 Dec 2009, assessed approximately up to 4 years.)

	Phase I: Dose Level 0	Phase I: Dose Level 1	Phase I: Dose Level 1A	Phase I: Dose Level 1B	Phase I: Dose Level 1C	Phase I: Dose Level 1D	Phase I: Dose Level 2	Phase I: Dose Level 3	Phase I: Dose Level 4	Phase I: Dose Level 5
Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every

	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).
Number of Participants Analyzed [units: participants]	0	0	0	0	0	0	0	0	0	0
Phase I: Determination of the optimally tolerated regimen (OTR) (units: Participants)										

Secondary Outcome Result(s)

Phase I: Overall Response Rate (ORR)

(Time Frame: From first initiated treatment on 19-Jan-2006 to the data cut-off date for primary CSR on 9 Dec 2009, assessed approximately up to 4 years.)

	Phase I: Dose Level 0	Phase I: Dose Level 1	Phase I: Dose Level 1A	Phase I: Dose Level 1B	Phase I: Dose Level 1C	Phase I: Dose Level 1D	Phase I: Dose Level 2	Phase I: Dose Level 3	Phase I: Dose Level 4	Phase I: Dose Level 5
Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).
Number of Participants Analyzed [units: participants]	6	2	10	4	3	3	3	5	6	3
Phase I: Overall Response Rate (ORR) (units: Percentage of Participants) Number (95% Confidence Interval)										
Best Response with Bone Scan Confirmation	67 (22.3 to 95.7)	50 (1.3 to 98.7)	30 (6.7 to 65.2)		67 (9.4 to 99.2)	33 (0.8 to 90.6)	33 (0.8 to 90.6)	40 (5.3 to 85.3)	33 (4.3 to 77.7)	

Best Response without Bone Scan Confirmation	67 (22.3 to 95.7)	100 (15.8 to 100.0)	60 (26.2 to 87.8)	25 (0.6 to 80.6)	100 (29.2 to 100.0)	67 (9.4 to 99.2)	33 (0.8 to 90.6)	100 (47.8 to 100.0)	83 (35.9 to 99.6)	67 (9.4 to 99.2)

Phase I: Duration of Response (DoR)

(Time Frame: From first initiated treatment on 19-Jan-2006 to the data cut-off date for primary CSR on 9 Dec 2009, assessed approximately up to 4 years.)

	Phase I: Dose Level 0	Phase I: Dose Level 1	Phase I: Dose Level 1A	Phase I: Dose Level 1B	Phase I: Dose Level 1C	Phase I: Dose Level 1D	Phase I: Dose Level 2	Phase I: Dose Level 3	Phase I: Dose Level 4	Phase I: Dose Level 5
Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).
Number of Participants Analyzed [units: participants]	4	2	6	1	3	2	1	5	5	2

Phase I: Duration of Response (DoR) (units: Weeks) Median (Inter-Quartile Range)	31.1 (24.9 to 184.4)	117.0 (108.3 to 125.7)	203.9 (143.3 to 241.7)	NA (NA to NA)[1]	54.1 (42.6 to 62.1)	77.1 (60.7 to 93.6)	64.3 (64.3 to 64.3)	61.6 (31.1 to 152.1)	NA (39.3 to NA)[23]	NA (57.0 to NA)[23]

[1] Not estimable due to censored data.
[2] Only first quartile estimable
[3] Only first quartile estimable

Phase I: Time to Response

(Time Frame: Week 8, Week 12, Week 16, Week 24, Week 32)

	Phase I: Dose Level 0	**Phase I: Dose Level 1**	**Phase I: Dose Level 1A**	**Phase I: Dose Level 1B**	**Phase I: Dose Level 1C**	**Phase I: Dose Level 1D**	**Phase I: Dose Level 2**	**Phase I: Dose Level 3**	**Phase I: Dose Level 4**	**Phase I: Dose Level 5**
Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg

	once a week).	once a week).	once a week).	once a week).	once a week).	once a week).	once a week).	once a week).	once a week).	once a week).
Number of Participants Analyzed [units: participants]	4	2	6	1	3	2	1	5	5	2
Phase I: Time to Response (units: Participants) Count of Participants (Not Applicable)										
CR or PR by Week 8	2 (50%)	0 (%)	3 (50%)	1 (100%)	2 (66.67%)	1 (50%)	1 (100%)	3 (60%)	4 (80%)	1 (50%)
CR or PR by Week 12	1 (25%)	1 (50%)	1 (16.67%)	0 (%)	0 (%)	0 (%)	0 (%)	2 (40%)	1 (20%)	0 (%)
CR or PR by Week 16	1 (25%)	1 (50%)	1 (16.67%)	0 (%)	1 (33.33%)	1 (50%)	0 (%)	0 (%)	0 (%)	0 (%)
CR or PR by Week 24	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (50%)
CR or PR by Week 32	0 (%)	0 (%)	1 (16.67%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)

Phase I: Time to Progression

(Time Frame: From first initiated treatment on 19-Jan-2006 to the data cut-off date for primary CSR on 9 Dec 2009, assessed approximately up to 4 years.)

	Phase I: Dose Level 0	**Phase I: Dose Level 1**	**Phase I: Dose Level 1A**	**Phase I: Dose Level 1B**	**Phase I: Dose Level 1C**	**Phase I: Dose Level 1D**	**Phase I: Dose Level 2**	**Phase I: Dose Level 3**	**Phase I: Dose Level 4**	**Phase I: Dose Level 5**

Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).
Number of Participants Analyzed [units: participants]	6	2	9	3	3	2	5	5	2	2
Phase I: Time to Progression (units: Weeks) Median (Inter-Quartile Range)										
	34.1 (32.0 to 50.9)	137.9 (119.6 to NA)[123456]	148.5 (27.5 to NA)[123456]	54.9 (17.1 to NA)[123456]	67.1 (53.6 to NA)[123456]	86.6 (73.9 to 99.3)	71.4 (50.3 to 130.9)	113.7 (37.9 to 165.0)	NA (45.6 to NA)[123456]	66.0 (63.9 to NA)[123456]

[1] Not estimable due to censored data.
[2] Not estimable due to censored data.
[3] Not estimable due to censored data.
[4] Not estimable due to censored data.
[5] Not estimable due to censored data.
[6] Not estimable due to censored data.

Safety Results

All-Cause Mortality

	Phase I: Dose Level 0 N = 6	Phase I: Dose Level 1 N = 3	Phase I: Dose Level 1A N = 12	Phase I: Dose Level 1B N = 5	Phase I: Dose Level 1C N = 4	Phase I: Dose Level 1D N = 3	Phase I: Dose Level 2 N = 5	Phase I: Dose Level 3 N = 6	Phase I: Dose Level 4 N = 6	Phase I: Dose Level 5 N = 3
Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).

Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	From study treatment start date till 30 days safety follow-up, assessed approximately up to 17 years.
Additional Description	Any sign or symptom that occurs during the treatment period plus 30 days post-treatment.
Source Vocabulary for Table Default	MedDRA 25.0
Assessment Type for Table Default	Systematic Assessment

	Phase I: Dose Level 0 N = 6	**Phase I: Dose Level 1 N = 3**	**Phase I: Dose Level 1A N = 12**	**Phase I: Dose Level 1B N = 5**	**Phase I: Dose Level 1C N = 4**	**Phase I: Dose Level 1D N = 3**	**Phase I: Dose Level 2 N = 5**	**Phase I: Dose Level 3 N = 6**	**Phase I: Dose Level 4 N = 6**	**Phase I: Dose Level 5 N = 3**
Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week,

	2mg/kg once a week).	2mg/kg once a week).	2mg/kg once a week).	2mg/kg once a week).	2mg/kg once a week).	2mg/kg once a week).	2mg/kg once a week).	2mg/kg once a week).	2mg/kg once a week).	2mg/kg once a week).
Total participants affected	1 (16.67%)	2 (66.67%)	6 (50.00%)	1 (20.00%)	0 (0.00%)	1 (33.33%)	4 (80.00%)	5 (83.33%)	3 (50.00%)	2 (66.67%)
Blood and lymphatic system disorders										
Febrile neutropenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Leukopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neutropenia	0 (0.00%)	1 (33.33%)	5 (41.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (60.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Cardiac disorders										
Cardiac failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders										
Colitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Diarrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
General disorders and administration site conditions										
Fatigue	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Mucosal inflammation	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyrexia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Infections and infestations										
Cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Lower respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Neutropenic sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular device infection	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Injury, poisoning and procedural complications										
Urinary retention postoperative	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Investigations										
Blood calcium increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ejection fraction decreased	0 (0.00%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)
Haemoglobin decreased	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oxygen saturation decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Nervous system disorders										
Transient ischaemic attack	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders										
Emphysema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumothorax	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders										
Rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	From study treatment start date till 30 days safety follow-up, assessed approximately up to 17 years.
Additional Description	Any sign or symptom that occurs during the treatment period plus 30 days post-treatment.
Source Vocabulary for Table Default	MedDRA 25.0
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Phase I: Dose Level 0 N = 6	Phase I: Dose Level 1 N = 3	Phase I: Dose Level 1A N = 12	Phase I: Dose Level 1B N = 5	Phase I: Dose Level 1C N = 4	Phase I: Dose Level 1D N = 3	Phase I: Dose Level 2 N = 5	Phase I: Dose Level 3 N = 6	Phase I: Dose Level 4 N = 6	Phase I: Dose Level 5 N = 3
Arm/Group Description	Lapatinib 500 mg once daily (OD) with Docetaxel 60 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1500 mg once daily (OD) with Docetaxel 75 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 500 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 750 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1000 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).	Lapatinib 1250 mg once daily (OD) with Docetaxel 100 mg/m2 once every 3 weekly (q3weeks) with Trastuzumab (Loading dose: 4mg/kg during first week, 2mg/kg once a week).
Total participants affected	6 (100.00 %)	3 (100.00 %)	12 (100.00 %)	5 (100.00 %)	4 (100.00 %)	3 (100.00 %)	5 (100.00 %)	6 (100.00 %)	6 (100.00 %)	3 (100.00 %)
Blood and lymphatic system disorders										
Anaemia	2 (33.33%)	0 (0.00%)	5 (41.67%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Leukopenia	1 (16.67%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neutropenia	4 (66.67%)	3 (100.00 %)	6 (50.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Splenic vein thrombosis	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Thrombocytopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Cardiac disorders										
Intracardiac mass	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Palpitations	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders										
Ear disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ear pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Vertigo	0 (0.00%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)
Eye disorders										
Conjunctival haemorrhage	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Conjunctival irritation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Dry eye	0 (0.00%)	1 (33.33%)	3 (25.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Erythema of eyelid	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Eye pain	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Eyelid oedema	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Foreign body sensation in eyes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Lacrimation increased	2 (33.33%)	2 (66.67%)	2 (16.67%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	4 (66.67%)	1 (33.33%)

Ocular hyperaemia	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Orbital oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Photopsia	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Scintillating scotoma	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vision blurred	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Visual acuity reduced	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Visual impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders										
Abdominal distension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain	4 (66.67%)	1 (33.33%)	4 (33.33%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (16.67%)	0 (0.00%)
Abdominal pain upper	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Aerophagia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anal fissure	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Anal haemorrhage	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aphthous ulcer	1 (16.67%)	1 (33.33%)	4 (33.33%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Breath odour	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Constipation	3 (50.00%)	0 (0.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	2 (40.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)
Diarrhoea	5 (83.33%)	3 (100.00 %)	11 (91.67%)	5 (100.00 %)	4 (100.00 %)	3 (100.00 %)	3 (60.00%)	5 (83.33%)	5 (83.33%)	2 (66.67%)
Dry mouth	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Dyschezia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)

Dyspepsia	1 (16.67%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	2 (40.00%)	2 (33.33%)	1 (16.67%)	0 (0.00%)
Dysphagia	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Gastritis	1 (16.67%)	1 (33.33%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)
Gastrooesophageal reflux disease	1 (16.67%)	0 (0.00%)	4 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Gingival bleeding	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gingival pain	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haematochezia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemorrhoids	1 (16.67%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)
Hiatus hernia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypoaesthesia oral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Intestinal obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lip pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mesenteric vein thrombosis	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mouth ulceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Nausea	3 (50.00%)	2 (66.67%)	7 (58.33%)	4 (80.00%)	4 (100.00 %)	2 (66.67%)	3 (60.00%)	5 (83.33%)	5 (83.33%)	3 (100.00 %)
Noninfective gingivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Odynophagia	1 (16.67%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Oesophagitis	0 (0.00%)	1 (33.33%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oral mucosal blistering	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oral pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)

Periodontal disease	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rectal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Stomatitis	3 (50.00%)	1 (33.33%)	2 (16.67%)	0 (0.00%)	3 (75.00%)	0 (0.00%)	3 (60.00%)	2 (33.33%)	1 (16.67%)	0 (0.00%)
Tongue ulceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Toothache	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (33.33%)
Vomiting	2 (33.33%)	2 (66.67%)	5 (41.67%)	1 (20.00%)	3 (75.00%)	0 (0.00%)	1 (20.00%)	4 (66.67%)	2 (33.33%)	3 (100.00 %)
General disorders and administration site conditions										
Asthenia	1 (16.67%)	1 (33.33%)	7 (58.33%)	2 (40.00%)	2 (50.00%)	1 (33.33%)	2 (40.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)
Axillary pain	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Catheter site bruise	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Catheter site erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Catheter site haematoma	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Catheter site inflammation	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Catheter site pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Chest discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Chest pain	0 (0.00%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Face oedema	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)

Fatigue	4 (66.67%)	3 (100.00 %)	3 (25.00%)	1 (20.00%)	2 (50.00%)	2 (66.67%)	3 (60.00%)	5 (83.33%)	3 (50.00%)	3 (100.00 %)
General physical health deterioration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Granuloma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Hypothermia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Influenza like illness	0 (0.00%)	2 (66.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infusion site vesicles	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Injection site erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injection site haemorrhage	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injection site rash	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mucosal dryness	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mucosal inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Nodule	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Oedema	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (16.67%)	0 (0.00%)
Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (33.33%)
Peripheral swelling	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyrexia	0 (0.00%)	1 (33.33%)	5 (41.67%)	2 (40.00%)	2 (50.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	1 (33.33%)

Xerosis	0 (0.00%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune system disorders										
Drug hypersensitivity	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	1 (33.33%)
Hypersensitivity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Infections and infestations										
Bronchitis	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	2 (16.67%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	3 (50.00%)	0 (0.00%)	0 (0.00%)
Cystitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Dermatitis infected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ear infection	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Eye infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Folliculitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Fungal foot infection	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fungal skin infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastroenteritis	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Herpes virus infection	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes zoster	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hordeolum	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infected cyst	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Influenza	1 (16.67%)	0 (0.00%)	3 (25.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Laryngitis	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Localised infection	1 (16.67%)	1 (33.33%)	0 (0.00%)	1 (20.00%)	1 (25.00%)	1 (33.33%)	1 (20.00%)	1 (16.67%)	2 (33.33%)	1 (33.33%)
Lower respiratory tract infection	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	3 (50.00%)	1 (16.67%)	0 (0.00%)
Mastitis	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nail bed infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Nail infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Nasopharyngitis	0 (0.00%)	2 (66.67%)	7 (58.33%)	1 (20.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (66.67%)
Oral herpes	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Paronychia	1 (16.67%)	2 (66.67%)	2 (16.67%)	2 (40.00%)	3 (75.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)
Pharyngitis	1 (16.67%)	1 (33.33%)	1 (8.33%)	1 (20.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Pustule	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash pustular	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory tract infection	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (33.33%)
Rhinitis	0 (0.00%)	0 (0.00%)	3 (25.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)
Sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Septic rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Sinusitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Skin infection	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tooth abscess	1 (16.67%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Tooth infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tracheitis	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	1 (20.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Urinary tract infection	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	3 (60.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaginal infection	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Vascular device infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (33.33%)
Vulvovaginal candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications										
Arthropod bite	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Fall	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pelvic fracture	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post procedural complication	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Procedural pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (50.00%)	1 (33.33%)
Radiation skin injury	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin laceration	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Thermal burn	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Wound secretion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Investigations										
Alanine aminotransferase	0 (0.00%)	1 (33.33%)	1 (8.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)

Alanine aminotransferase increased	0 (0.00%)	0 (0.00%)	2 (16.67%)	2 (40.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	2 (33.33%)	1 (16.67%)	0 (0.00%)
Aspartate aminotransferase	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Aspartate aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	2 (33.33%)	1 (16.67%)	0 (0.00%)
Blood albumin decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Blood alkaline phosphatase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Blood bilirubin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Blood calcium decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Blood glucose increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Blood magnesium decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Ejection fraction decreased	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gamma-glutamyltransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Haemoglobin decreased	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	2 (33.33%)	1 (16.67%)	2 (66.67%)
Weight decreased	0 (0.00%)	1 (33.33%)	1 (8.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (66.67%)

White blood cell count decreased	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders										
Decreased appetite	0 (0.00%)	1 (33.33%)	4 (33.33%)	2 (40.00%)	3 (75.00%)	0 (0.00%)	2 (40.00%)	1 (16.67%)	1 (16.67%)	2 (66.67%)
Dehydration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Hyperglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypoglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyponatraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Musculoskeletal and connective tissue disorders										
Arthralgia	2 (33.33%)	1 (33.33%)	7 (58.33%)	2 (40.00%)	2 (50.00%)	1 (33.33%)	1 (20.00%)	2 (33.33%)	4 (66.67%)	1 (33.33%)
Arthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Back pain	1 (16.67%)	3 (100.00 %)	3 (25.00%)	1 (20.00%)	1 (25.00%)	2 (66.67%)	1 (20.00%)	1 (16.67%)	1 (16.67%)	2 (66.67%)
Bone pain	0 (0.00%)	0 (0.00%)	3 (25.00%)	2 (40.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (33.33%)	2 (66.67%)
Joint swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle spasms	0 (0.00%)	0 (0.00%)	4 (33.33%)	1 (20.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Muscular weakness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Musculoskeletal chest pain	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Musculoskeletal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal pain	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myalgia	1 (16.67%)	0 (0.00%)	4 (33.33%)	2 (40.00%)	2 (50.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	2 (33.33%)	1 (33.33%)
Neck pain	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Osteonecrosis	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Osteopenia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain in extremity	2 (33.33%)	0 (0.00%)	2 (16.67%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	4 (66.67%)	1 (16.67%)	0 (0.00%)
Pain in jaw	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spinal pain	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Systemic lupus erythematosus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
Cancer pain	0 (0.00%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders										
Ageusia	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Allodynia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Coma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Dizziness	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (33.33%)	1 (20.00%)	2 (33.33%)	0 (0.00%)	1 (33.33%)
Dysgeusia	1 (16.67%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	2 (50.00%)	1 (33.33%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Electric shock sensation	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Headache	4 (66.67%)	2 (66.67%)	6 (50.00%)	1 (20.00%)	3 (75.00%)	1 (33.33%)	1 (20.00%)	2 (33.33%)	2 (33.33%)	1 (33.33%)

Horner's syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Hyperaesthesia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypoaesthesia	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Memory impairment	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Migraine	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Motor dysfunction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Neuralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neuropathy peripheral	3 (50.00%)	0 (0.00%)	3 (25.00%)	1 (20.00%)	0 (0.00%)	2 (66.67%)	2 (40.00%)	2 (33.33%)	5 (83.33%)	2 (66.67%)
Paraesthesia	1 (16.67%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Peripheral sensory neuropathy	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Presyncope	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Restless legs syndrome	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sciatica	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Seizure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Taste disorder	4 (66.67%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	2 (50.00%)	0 (0.00%)	2 (40.00%)	1 (16.67%)	3 (50.00%)	2 (66.67%)
Psychiatric disorders										
Abnormal dreams	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Anxiety	1 (16.67%)	1 (33.33%)	3 (25.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (66.67%)

Confusional state	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depression	1 (16.67%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Insomnia	5 (83.33%)	1 (33.33%)	3 (25.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	2 (33.33%)	0 (0.00%)	2 (66.67%)
Mood altered	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Tearfulness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders										
Dysuria	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neurogenic bladder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Pollakiuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Urinary incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary retention	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Reproductive system and breast disorders										
Amenorrhoea	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Breast oedema	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Breast pain	1 (16.67%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Genital haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intermenstrual bleeding	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Menopausal symptoms	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Pelvic pain	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Vaginal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Vulvovaginal dryness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vulvovaginal pruritus	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders										
Allergic sinusitis	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cough	0 (0.00%)	2 (66.67%)	4 (33.33%)	3 (60.00%)	2 (50.00%)	1 (33.33%)	1 (20.00%)	5 (83.33%)	1 (16.67%)	0 (0.00%)
Dysphonia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (33.33%)
Dyspnoea	1 (16.67%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	3 (50.00%)	2 (33.33%)	0 (0.00%)
Dyspnoea exertional	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Emphysema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epistaxis	2 (33.33%)	2 (66.67%)	6 (50.00%)	2 (40.00%)	3 (75.00%)	1 (33.33%)	3 (60.00%)	3 (50.00%)	2 (33.33%)	1 (33.33%)
Nasal congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasal dryness	0 (0.00%)	1 (33.33%)	2 (16.67%)	1 (20.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Nasal inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)
Nasal obstruction	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oropharyngeal pain	1 (16.67%)	1 (33.33%)	2 (16.67%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	2 (40.00%)	3 (50.00%)	2 (33.33%)	1 (33.33%)
Pharyngeal erythema	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Pharyngeal oedema	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pleural effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Productive cough	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary fibrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rhinorrhoea	1 (16.67%)	2 (66.67%)	7 (58.33%)	1 (20.00%)	2 (50.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)
Sinus congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tachypnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Skin and subcutaneous tissue disorders										
Acne	1 (16.67%)	0 (0.00%)	3 (25.00%)	2 (40.00%)	3 (75.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (16.67%)	0 (0.00%)
Alopecia	4 (66.67%)	2 (66.67%)	6 (50.00%)	3 (60.00%)	4 (100.00 %)	2 (66.67%)	5 (100.00 %)	4 (66.67%)	4 (66.67%)	3 (100.00 %)
Blister	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dermatitis acneiform	0 (0.00%)	0 (0.00%)	5 (41.67%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	1 (33.33%)
Dermatitis allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Drug eruption	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dry skin	1 (16.67%)	2 (66.67%)	3 (25.00%)	1 (20.00%)	2 (50.00%)	0 (0.00%)	2 (40.00%)	4 (66.67%)	1 (16.67%)	1 (33.33%)
Ecchymosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eczema	1 (16.67%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Erythema	1 (16.67%)	1 (33.33%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (16.67%)	2 (33.33%)	0 (0.00%)
Nail disorder	2 (33.33%)	2 (66.67%)	6 (50.00%)	1 (20.00%)	4 (100.00 %)	2 (66.67%)	1 (20.00%)	3 (50.00%)	4 (66.67%)	1 (33.33%)

Nail ridging	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	1 (33.33%)
Nail toxicity	0 (0.00%)	1 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Onychalgia	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Onychoclasis	1 (16.67%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Onycholysis	1 (16.67%)	2 (66.67%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (16.67%)	1 (33.33%)
Onychomadesis	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain of skin	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.00%)	0 (0.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Pruritus	2 (33.33%)	3 (100.00 %)	4 (33.33%)	1 (20.00%)	1 (25.00%)	1 (33.33%)	0 (0.00%)	3 (50.00%)	1 (16.67%)	0 (0.00%)
Pruritus allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Purpura	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Rash	4 (66.67%)	2 (66.67%)	5 (41.67%)	1 (20.00%)	4 (100.00 %)	2 (66.67%)	2 (40.00%)	4 (66.67%)	4 (66.67%)	1 (33.33%)
Rash erythematous	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash macular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (50.00%)	1 (33.33%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash papular	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash pruritic	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Scab	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Skin discolouration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Skin disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin exfoliation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)

Skin fissures	1 (16.67%)	2 (66.67%)	3 (25.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)
Vascular skin disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Xeroderma	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Social circumstances										
Menopause	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Surgical and medical procedures										
Cataract operation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Vascular disorders										
Hot flush	1 (16.67%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Hypertension	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypotension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Hypovolaemic shock	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Lymphoedema	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thrombophlebitis	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

Based on the Primary CSR, 2 dose levels of lapatinib with docetaxel and trastuzumab were suggested based on the overall toxicity profile: lapatinib 1250mg - docetaxel 75mg/m² with trastuzumab or lapatinib 1000mg - docetaxel 100mg/m² with trastuzumab.

Overall, the combination of lapatinib, docetaxel and trastuzumab used in this long-term follow-up study was manageable and well tolerated within the limited subjects studied in this protocol. There were no new safety concerns identified in this study.

Overall, the key secondary efficacy results and safety results were consistent with what were reported in the primary CSR.

Date of Clinical Trial Report

16-Feb-2023