Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ribociclib

Trial Indication(s)

Treatment of postmenopausal women with hormone receptor positive, HER2 negative locally recurrent or advanced metastatic breast cancer

Protocol Number

CLEE011X2108

Protocol Title

A phase Ib/II study of LEE011 in combination with fulvestrant and BYL719 or BKM120 in the treatment of postmenopausal women with hormone receptor positive, HER2 negative locally recurrent or advanced metastatic breast cancer

Clinical Trial Phase

Phase 1/Phase 2

Phase of Drug Development

Approved

Study Start/End Dates

Study Start Date: May 2014 (Actual)

Primary Completion Date: April 2018 (Actual)
Study Completion Date: April 2018 (Actual)

Reason for Termination (If applicable)

Based upon Novartis business decisions, the expansion/Phase II was not opened.

Study Design/Methodology

This was an open-label, multi-center Phase Ib/II study. The Phase Ib dose escalation was conducted for the two triple combinations arms (Arm 1 and Arm 2) and dose confirmation for the two double combination arms (Arm 3 and Arm 3A).
The Phase II part of the study was planned but not conducted based on the emergence of higher than expected adverse events in the triple combinations and as a result, the expansion/Phase II was not opened.

Centers

11 centers in 8 countries: Spain(1), France(1), Italy(2), Singapore(1), Taiwan(1), United States(3), Korea, Republic of(1), United Kingdom(1)

Objectives:

Primary Objectives for Phase Ib:
To estimate the Maximum Tolerated Dose (MTD) and/or Recommended Phase II Dose (RP2D) and schedule of the following two combinations in patients with HR-positive/HER2-negative advanced BC.

- LEE011 + BKM120 + fulvestrant (Arm 1)
- LEE011 + BYL719 + fulvestrant (Arm 2)

In addition, to confirm the safety of the doublet arms (Arms 3 and 3A):

- LEE011 (3 weeks on, 1 week off) + fulvestrant (Arm 3)
- LEE011 (continuous daily dosing) + fulvestrant (Arm 3A)

Secondary Objectives for Phase Ib:

- To characterize the safety and tolerability of LEE011 + BKM120 + fulvestrant, LEE011 + BYL719 + fulvestrant and LEE011 (3 weeks on, 1 week off, or continuous daily dosing) + fulvestrant.
- To characterize the pharmacokinetic (PK) properties of LEE011, BKM120, BYL719 within thecombinations studied and to compare across treatment arms; as well as to evaluate trough levels of fulvestrant in each combination and any other clinically significant metabolites that
  may be identified.
- To assess preliminary clinical anti-tumor activity of LEE011 + BKM120 + fulvestrant, LEE011 + BYL719 + fulvestrant, LEE011 (3 weeks on, 1 week off, or continuous daily dosing) +fulvestrant.

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

In Arm1, Arm 2, Arm 3, and Arm 3A “investigational or study drug” refers to Novartis study drugs LEE011(ribociclib), BKM120 and BYL719, which were packaged and supplied by Novartis Drug Supply Management.

- Ribociclib (LEE011) was supplied as 50 mg and 200 mg capsules for oral administration.
- BKM120 was supplied as 10 mg and 50 mg hard gelatin capsules for oral administration.
- BYL719 was supplied as 50 mg and 200 mg tablets for oral administration. All oral medications were packaged in bottles.
- Fulvestrant was supplied through BAP Pharma.

A listing of patients receiving each batch of test material was provided in Appendix 16.1.6.

Statistical Methods

- The primary variable was the incidence of DLTs in Cycle 1. An adaptive Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle was used during the dose escalation phase to guide the dose recommendation for next cohorts, including the MTD and/or RP2D, using the dose-determining set.
- Efficacy analyses included best overall response, overall response rate (ORR) and progression free survival (PFS). The best percentage change from baseline in sum of longest diameters (SLD) in target lesions together with best overall response was presented using waterfall plot. These endpoints were analyzed by treatment group using the FAS
- Analyses of safety data were done by treatment group using the safety set. Summary tables of treatment-emergent AE, including type of event and relation to study treatment, SAE, results of laboratory tests, .ECG and Vital signs were presented. Information reported prior- and/or post-treatment period was included in listings, as applicable.
- Pharmacokinetic analysis set (PAS) was used for PK analysis. Descriptive statistics were presented for primary and secondary PK parameters by analyte, treatment group, and study day.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Postmenopausal, Hormone receptor positive (HR+), HER2 negative breast cancer
- Unlimited number of lines of endocrine therapy and up to two lines of cytotoxic chemotherapy in the metastatic setting (Phase Ib)
- Unlimited number of lines of endocrine therapy and one line of cytotoxic chemotherapy in the metastatic setting (Phase II)

Exclusion Criteria:
- HER2-overexpression in the patient's tumor tissue
- Inadequate bone marrow function or evidence of end-organ damage
- Severe or uncontrolled medical issues
- Diabetes mellitus

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	LEE011 600 mg + fulvestrant	LEE011 400mg cont. + fulvestrant	LEE011 + BYL719 + fulvestrant	LEE011 + BKM120 + fulvestrant	Total
Arm/Group Description	LEE011 - 28 day cycles (3 weeks on, 1 week off), fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (continuous daily dosing - dose escalating) fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BYL719 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BKM120 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	
Started	13	15	18	24	70

Completed	0	2	1	3	6
Not Completed	13	13	17	21	64
Withdrawal by Subject	0	0	1	2	3
progressive disease	11	9	12	17	49
Physician Decision	1	2	0	0	3
Adverse Event	1	2	4	2	9

Baseline Characteristics

	LEE011 600 mg + fulvestrant	**LEE011 400mg cont. + fulvestrant**	**LEE011 + BYL719 + fulvestrant**	**LEE011 + BKM120 + fulvestrant**	**Total**
Arm/Group Description	LEE011 - 28 day cycles (3 weeks on, 1 week off), fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (continuous daily dosing - dose escalating) fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BYL719 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BYL719 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	

Number of Participants [units: participants]	13	15	18	24	70
Age Continuous (units: years) Mean ± Standard Deviation					
	59.5±8.02	57.5±8.81	60.3±11.69	56.5±10.21	58.3±9.90
Race/Ethnicity, Customized[1] (units: participants) Count of Participants (Not Applicable)					
Asian	2	3	5	10	20
Black or African	0	1	0	0	1
Unknown	2	0	0	3	5
White	9	11	13	11	44
Race/Ethnicity, Customized[2] (units: participants) Count of Participants (Not Applicable)					
not Hispanic or Latino	6	10	16	14	46
Not reported	7	3	2	8	20
unknown	0	2	0	2	4
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)					
Female	13	15	18	24	70
Male	0	0	0	0	0

[1] Race
[2] Ethnicity

Summary of Efficacy

Primary Outcome Result(s)

Incidence of Dose limiting toxicities (DLTs) - Phase Ib only

(Time Frame: 28 days)

	LEE011 600 mg + fulvestrant	LEE011 400mg cont. + fulvestrant	LEE011 + BYL719 + fulvestrant	LEE011 + BKM120 + fulvestrant
Arm/Group Description	LEE011 - 28 day cycles (3 weeks on, 1 week off), fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (continuous daily dosing - dose escalating) fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BYL719 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BYL719 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.
Number of Participants Analyzed [units: participants]	13	15	15	21
Incidence of Dose limiting toxicities (DLTs) - Phase Ib only (units: participants) Count of Participants (Not Applicable)				
	1	1	5	5

Secondary Outcome Result(s)

Plasma concentration-time profiles of LEE011, BKM120, BYL719

(Time Frame: Day 21)

	LEE011 400mg+BKM120 30mg+Fulvestrant	LEE011 400mg+BKM120 40mg+Fulvestrant	LEE011 600mg+BKM120 30mg+Fulvestrant	LEE011 + BYL719 200mg+ fulvestrant	LEE011 400mg+BYL719 150mg+Fulvestrant	LEE011 400mg+BYL719 200mg+Fulvestrant	LEE011 600 mg + fulvestrant	LEE011 400mg cont. + fulvestrant
Arm/Group Description	LEE011 400mg+BKM120 30mg+Fulvestrant 500mg	LEE011 400mg+BKM120 40mg+Fulvestrant 500mg	LEE011 600mg+BKM120 30mg+Fulvestrant 500mg	LEE011 200mg+BYL719 200mg+Fulvestrant	LEE011 400mg+BYL719 150mg+Fulvestrant	LEE011 400mg+BYL719 200mg+Fulvestrant 500mg	LEE011 - 28 day cycles (3 weeks on, 1 week off), fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (continuous daily dosing - dose escalating) fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.
Number of Participants Analyzed [units: participants]	10	6	8	3	6	9	13	15

Plasma concentration-time profiles of LEE011, BKM120, BYL719
(units: ng/mL)
Geometric Mean (Geometric Coefficient of Variation)

LEE011	980 (40.8%)	1010 (67.5%)	2210 (36.0%)	284 (42.7%)	622 (33.7%)	960 (25.4%)	1840 (51.1 %)	1110 (50.9 %)
LEQ803 (LEE011 metabolite)	157 (46.3%)	95 (95.3%)	180 (3.5%)	47.1 (84.5%)	106 (18.9%)	107 (71.2%)	168 (66.1%)	105 (40.1%)
BYL719	0 (0%)	0 (0%)	0 (0%)	1860 (14.5%)	1730 (13.7%)	2130 (36.1%)	0 (0%)	0 (0%)
BKM120	769 (64.9%)	771 (60.0%)	482 (56.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Overall Response Rate (ORR)

(Time Frame: 36 months)

	LEE011 400mg cont. + fulvestrant	**LEE011 600 mg + fulvestrant**	**LEE011 + BYL719 + fulvestrant**	**LEE011 + BKM120 + fulvestrant**
Arm/Group Description	LEE011 - 28 day cycles (continuous daily dosing - dose escalating) fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (3 weeks on, 1 week off), fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BYL719 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BYL719 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.
Number of Participants Analyzed [units: participants]	15	13	18	24
Overall Response Rate (ORR) (units: participants)				

Count of Participants (Not Applicable)				
	2	3	3	6

Progression Free Survival (PFS) (phase I only)

(Time Frame: 24 months)

	LEE011 600 mg + fulvestrant	LEE011 400mg cont. + fulvestrant	LEE011 + BYL719 + fulvestrant	LEE011 + BKM120 + fulvestrant
Arm/Group Description	LEE011 - 28 day cycles (3 weeks on, 1 week off), fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (continuous daily dosing - dose escalating) fulvestrant - 500 mg i.m. given on Day 1 and Day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BYL719 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.	LEE011 - 28 day cycles (21 days followed by a 7 day break - dose escalating) BYL719 - daily (dose escalating) fulvestrant - i.m. - 500 mg given on day 1 and day 15 of Cycle 1, then on Day 1 of each subsequent cycle.
Number of Participants Analyzed [units: participants]	13	15	18	24
Progression Free Survival (PFS) (phase I only) (units: participants) Count of Participants (Not Applicable)				
	11	9	12	17

Summary of Safety

Safety Results

All-Cause Mortality

	LEE011 600mg+ Fulvestrant N = 13	LEE011 400mg (cont.)+ @Fulvestrant N = 15	LEE011 200mg+ @BYL719 200mg+ @Fulvestrant N = 3	LEE011 400mg+ @BYL719 150mg+ @Fulvestrant N = 6	LEE011 400mg+ @BYL719 200mg+ @Fulvestrant N = 9	LEE011 400mg+ @BKM120 30mg+@ Fulvestrant N = 10	LEE011 400mg+ @BKM120 40mg+@ Fulvestrant N = 6	LEE011 600mg+ @BKM120 30mg+@ Fulvestrant N = 8	All subjects@(doublets)@LEE+ Fulvestrant N = 28	All subjects@(triplets)@LEE + BYL + Fulvestrant N = 18	All subjects@(triplets)@LEE + BKM + Fulvestrant N = 24	All@subjects N = 70
Arm/ Group Description	LEE011 600mg+ Fulvestrant	LEE011 400mg (cont.)+ @Fulvestrant	LEE011 200mg+ @BYL719 200mg+ @Fulvestrant	LEE011 400mg+ @BYL719 150mg+ @Fulvestrant	LEE011 400mg+ @BYL719 200mg+ @Fulvestrant	LEE011 400mg+ @BKM120 30mg+@ Fulvestrant	LEE011 400mg+ @BKM120 40mg+@ Fulvestrant	LEE011 600mg+ @BKM120 30mg+@ Fulvestrant	All subjects@(doublets)@LEE+ Fulvestrant	All subjects@(triplets)@LEE + BYL + Fulvestrant	All subjects@(triplets)@LEE + BKM + Fulvestrant	All@subjects
Total participants affected	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	up to 24 months
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment

	LEE011 600mg+ Fulvestrant N = 13	**LEE011 400mg (cont.)+ @Fulvestrant N = 15**	**LEE011 200mg+ @BYL719 200mg+ @Fulvestrant N = 3**	**LEE011 400mg+ @BYL719 150mg+ @Fulvestrant N = 6**	**LEE011 400mg+ @BYL719 200mg+ @Fulvestrant N = 9**	**LEE011 400mg+ @BKM120 30mg+ @Fulvestrant N = 10**	**LEE011 400mg+ @BKM120 40mg+ @Fulvestrant N = 6**	**LEE011 600mg+ @BKM120 30mg+ @Fulvestrant N = 8**	**All subjects@(doublets)@LEE+ Fulvestrant N = 28**	**All subjects@(triplets)@LEE + BYL + Fulvestrant N = 18**	**All subjects@(triplets)@LEE + BKM + Fulvestrant N = 24**	**All@subjects N = 70**
Arm/Group Description	LEE011 600mg+ Fulvestrant	LEE011 400mg (cont.)+ @Fulvestrant	LEE011 200mg+ @BYL719 200mg+ @Fulvestrant	LEE011 400mg+ @BYL719 150mg+ @Fulvestrant	LEE011 400mg+ @BYL719 200mg+ @Fulvestrant	LEE011 400mg+ @BKM120 30mg+@ Fulvestrant	LEE011 400mg+ @BKM120 40mg+@ Fulvestrant	LEE011 600mg+ @BKM120 30mg+@ Fulvestrant	All subjects@(doublets)@LEE+ Fulvestrant	All subjects@(triplets)@LEE + BYL + Fulvestrant	All subjects@(triplets)@LEE + BKM + Fulvestrant	All@subjects
Total participants affected	8 (61.54 %)	3 (20.00 %)	0 (0.00%)	3 (50.00 %)	3 (33.33 %)	3 (30.00 %)	2 (33.33 %)	4 (50.00 %)	11 (39.29%)	6 (33.33%)	9 (37.50%)	26 (37.14 %)
Blood and lymphatic system disorders												
Leukopenia	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Neutropenia	2 (15.38%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	3 (10.71%)	0 (0.00%)	1 (4.17%)	4 (5.71%)
Cardiac disorders												
Atrial fibrillation	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Gastrointestinal disorders												
Nausea	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Small intestinal obstruction	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Vomiting	2 (15.38%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	1 (4.17%)	3 (4.29%)
General disorders and administration site conditions												
Fatigue	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Non-cardiac	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)

chest pain												
Pyrexia	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (25.00%)	1 (3.57%)	0 (0.00%)	2 (8.33%)	3 (4.29%)
Hepatobiliary disorders												
Drug-induced liver injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Hepatic function abnormal	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Infections and infestations												
Bronchitis	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pneumonia	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (5.56%)	1 (4.17%)	3 (4.29%)
Pyelonephritis acute	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%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Urinary tract	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.86%)

infection												
Varicella	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Injury, poisoning and procedural complications												
Overdose	2 (15.38%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Investigations												
Alanine aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Aspartate aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (4.17%)	2 (2.86%)
Musculoskeletal and connective tissue disorders												

Musculoskeletal chest pain	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pain in extremity	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Metastases to central nervous system	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Tumour pain	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Nervous system disorders												

Syncope	2 (15.38%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	1 (5.56%)	0 (0.00%)	3 (4.29%)
Psychiatric disorders												
Delirium	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Mental status changes	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Renal and urinary disorders												
Acute kidney injury	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%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Respiratory, thoracic and mediastinal disorders												
Dyspnoea	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Interstitial lung disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)

Pleural effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Pulmonary embolism	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Skin and subcutaneous tissue disorders												
Eczema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)

Other Adverse Events by System Organ Class

Time Frame	up to 24 months
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LEE011 600mg+	**LEE011 400mg**	**LEE011 200mg+**	**LEE011 400mg+**	**LEE011 400mg+**	**LEE011 400mg+**	**LEE011 400mg+**	**LEE011 600mg+**	**All subjects@(**	**All subjects@**	**All subjects@**	**All@ subje**

	Fulvestrant N = 13	(cont.)+@Fulvestrant N = 15	@BYL719 200mg+@Fulvestrant N = 3	@BYL719 150mg+@Fulvestrant N = 6	@BYL719 200mg+@Fulvestrant N = 9	@BKM120 30mg+@Fulvestrant N = 10	@BKM120 40mg+@Fulvestrant N = 6	@BKM120 30mg+@Fulvestrant N = 8	doublets)@LEE+Fulvestrant N = 28	(triplets)@LEE + BYL + Fulvestrant N = 18	(triplets)@LEE + BKM + Fulvestrant N = 24	cts N = 70
Arm/Group Description	LEE011 600mg+ Fulvestrant	LEE011 400mg (cont.)+ @Fulvestrant	LEE011 200mg+ @BYL719 200mg+ @Fulvestrant	LEE011 400mg+ @BYL719 150mg+ @Fulvestrant	LEE011 400mg+ @BYL719 200mg+ @Fulvestrant	LEE011 400mg+ @BKM120 30mg+ @Fulvestrant	LEE011 400mg+ @BKM120 40mg+ @Fulvestrant	LEE011 600mg+ @BKM120 30mg+ @Fulvestrant	All subjects@(doublets)@LEE+ Fulvestrant	All subjects@(triplets)@LEE + BYL + Fulvestrant	All subjects@(triplets)@LEE + BKM + Fulvestrant	All@subjects
Total participants affected	13 (100.00%)	15 (100.00%)	3 (100.00%)	6 (100.00%)	9 (100.00%)	10 (100.00%)	6 (100.00%)	8 (100.00%)	28 (100.00%)	18 (100.00%)	24 (100.00%)	70 (100.00%)
Blood and lymphatic system disorders												
Anaemia	6 (46.15%)	2 (13.33%)	0 (0.00%)	1 (16.67%)	2 (22.22%)	0 (0.00%)	1 (16.67%)	2 (25.00%)	8 (28.57%)	3 (16.67%)	3 (12.50%)	14 (20.00%)
Anaemia macrocytic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Increased tendency to bruise	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Leukopenia	1 (7.69%)	2 (13.33%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (12.50%)	3 (10.71%)	1 (5.56%)	2 (8.33%)	6 (8.57%)

Lympho penia	1 (7.69 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	0 (0.00%)	2 (2.8 6%)
Neutrop enia	10 (76.9 2%)	10 (66.67 %)	0 (0.00%)	1 (16.67 %)	7 (77.78 %)	8 (80.00 %)	4 (66.67 %)	5 (62.50 %)	20 (71.43%)	8 (44.44%)	17 (70.83 %)	45 (6 4.29 %)
Thromb ocytope nia	3 (23.08 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (55.56 %)	2 (20.00 %)	2 (33.33 %)	2 (25.00 %)	3 (10.71%)	5 (27.78%)	6 (25.00%)	14 (2 0.00 %)
Cardiac disorders												
Atrioven tricular block first degree	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Palpitati ons	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.8 6%)
Pericard ial effusion	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Sinus bradyca rdia	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.4 3%)
Suprave ntricular tachyca rdia	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Tachyc ardia	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.8 6%)
Endocrin e disorders												
Hypothy roidism	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.4 3%)

Eye disorders												
Asthenopia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Cataract	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Corneal deposits	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Dry eye	1 (7.69%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	1 (4.17%)	3 (4.29%)
Eye swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Lacrimation increased	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.86%)
Ocular hyperaemia	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%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Strabismus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Vision blurred	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (5.56%)	0 (0.00%)	2 (2.86%)
Gastrointestinal disorders												
Abdominal discomfort	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Abdominal distension	1 (7.69%)	1 (6.67%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	1 (5.56%)	0 (0.00%)	3 (4.29%)

Abdominal pain	1 (7.69 %)	5 (33.33 %)	2 (66.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	6 (21.43%)	2 (11.11%)	1 (4.17%)	9 (12. 86%)
Abdominal pain upper	2 (15.38 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	2 (7.14%)	0 (0.00%)	1 (4.17%)	3 (4.2 9%)
Aphthous ulcer	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Ascites	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.8 6%)
Bowel movement irregularity	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Constipation	1 (7.69 %)	4 (26.67 %)	2 (66.67 %)	2 (33.33 %)	1 (11.11 %)	2 (20.00 %)	1 (16.67 %)	1 (12.50 %)	5 (17.86%)	5 (27.78%)	4 (16.67%)	14 (2 0.00 %)
Diarrhoea	4 (30.77 %)	4 (26.67 %)	3 (100.00 %)	2 (33.33 %)	3 (33.33 %)	4 (40.00 %)	2 (33.33 %)	4 (50.00 %)	8 (28.57%)	8 (44.44%)	10 (41.67 %)	26 (3 7.14 %)
Dry mouth	0 (0.00 %)	2 (13.33 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	0 (0.00%)	2 (2.8 6%)
Dyspepsia	0 (0.00 %)	1 (6.67%)	1 (33.33 %)	1 (16.67 %)	3 (33.33 %)	1 (10.00 %)	2 (33.33 %)	1 (12.50 %)	1 (3.57%)	5 (27.78%)	4 (16.67%)	10 (1 4.29 %)
Dysphagia	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.8 6%)
Epigastric discomfort	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Eructation	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.8 6%)
Faeces soft	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.4 3%)

Flatulence	1 (7.69 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	1 (4.17%)	3 (4.29%)
Gastrooesophageal reflux disease	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	1 (10.00 %)	2 (33.33 %)	1 (12.50 %)	1 (3.57%)	1 (5.56%)	4 (16.67%)	6 (8.57%)
Haemorrhoids	1 (7.69 %)	1 (6.67%)	0 (0.00%)	2 (33.33 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	2 (11.11%)	0 (0.00%)	4 (5.71%)
Mouth ulceration	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Nausea	7 (53.85 %)	9 (60.00 %)	2 (66.67 %)	3 (50.00 %)	7 (77.78 %)	6 (60.00 %)	4 (66.67 %)	7 (87.50 %)	16 (57.14%)	12 (66.67 %)	17 (70.83 %)	45 (64.29 %)
Odynophagia	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Oesophagitis	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (4.17%)	2 (2.86%)
Oral pain	2 (15.38 %)	1 (6.67%)	1 (33.33 %)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	3 (10.71%)	1 (5.56%)	1 (4.17%)	5 (7.14%)
Stomatitis	0 (0.00 %)	3 (20.00 %)	1 (33.33 %)	0 (0.00%)	5 (55.56 %)	2 (20.00 %)	1 (16.67 %)	2 (25.00 %)	3 (10.71%)	6 (33.33%)	5 (20.83%)	14 (20.00 %)
Vomiting	5 (38.46 %)	3 (20.00 %)	2 (66.67 %)	1 (16.67 %)	2 (22.22 %)	4 (40.00 %)	2 (33.33 %)	2 (25.00 %)	8 (28.57%)	5 (27.78%)	8 (33.33%)	21 (30.00 %)
General disorders and administration site conditions												

Asthenia	1 (7.69 %)	3 (20.00 %)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	1 (10.00 %)	0 (0.00%)	1 (12.50 %)	4 (14.29%)	1 (5.56%)	2 (8.33%)	7 (10. 00%)
Catheter site dermatitis	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.4 3%)
Catheter site pain	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Catheter site pruritus	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Chest discomfort	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (22.22 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	2 (2.8 6%)
Chills	0 (0.00 %)	2 (13.33 %)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	2 (7.14%)	1 (5.56%)	1 (4.17%)	4 (5.7 1%)
Fatigue	9 (69.23 %)	8 (53.33 %)	1 (33.33 %)	3 (50.00 %)	6 (66.67 %)	6 (60.00 %)	4 (66.67 %)	4 (50.00 %)	17 (60.71%)	10 (55.56 %)	14 (58.33 %)	41 (5 8.57 %)
Gait disturbance	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (20.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.8 6%)
Impaired healing	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Influenza like illness	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.8 6%)
Injection site pain	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.8 6%)
Malaise	1 (7.69 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	2 (7.14%)	0 (0.00%)	1 (4.17%)	3 (4.2 9%)

Mucosal inflammation	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Non-cardiac chest pain	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.8 6%)
Oedema peripheral	0 (0.00 %)	2 (13.33 %)	0 (0.00%)	1 (16.67 %)	1 (11.11 %)	1 (10.00 %)	0 (0.00%)	1 (12.50 %)	2 (7.14%)	2 (11.11%)	2 (8.33%)	6 (8.5 7%)
Pain	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Peripheral swelling	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	1 (5.56%)	1 (4.17%)	2 (2.8 6%)
Pyrexia	3 (23.08 %)	2 (13.33 %)	0 (0.00%)	2 (33.33 %)	1 (11.11 %)	1 (10.00 %)	1 (16.67 %)	2 (25.00 %)	5 (17.86%)	3 (16.67%)	4 (16.67%)	12 (1 7.14 %)
Temperature intolerance	0 (0.00 %)	1 (6.67%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (5.56%)	0 (0.00%)	2 (2.8 6%)
Immune system disorders												
Contrast media reaction	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Drug hypersensitivity	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Infections and infestations												

Catheter site infection	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%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Conjunctivitis	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.86%)
Ear infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Ear infection fungal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Escherichia infection	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Escherichia urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Hepatitis B	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Herpes simplex	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Herpes virus infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Influenza	0 (0.00%)	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	1 (4.17%)	3 (4.29%)
Mastitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Nasopharyngitis	0 (0.00%)	2 (13.33%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (7.14%)	1 (5.56%)	1 (4.17%)	4 (5.71%)
Oral candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)

Oropharyngeal candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (4.17%)	2 (2.86%)
Tinea infection	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Tooth infection	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Upper respiratory tract infection	2 (15.38%)	1 (6.67%)	0 (0.00%)	1 (16.67%)	2 (22.22%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	3 (10.71%)	3 (16.67%)	1 (4.17%)	7 (10.00%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.86%)
Vulvovaginal candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Injury, poisoning and procedural complications												
Foot fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Infusion related reaction	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Overdose	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (5.56%)	1 (4.17%)	3 (4.29%)

Radiation pneumonitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Wound complication	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Investigations												
Alanine aminotransferase increased	4 (30.77%)	4 (26.67%)	2 (66.67%)	5 (83.33%)	1 (11.11%)	5 (50.00%)	3 (50.00%)	3 (37.50%)	8 (28.57%)	8 (44.44%)	11 (45.83%)	27 (38.57%)
Amylase increased	2 (15.38%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (12.50%)	2 (7.14%)	0 (0.00%)	2 (8.33%)	4 (5.71%)
Aspartate aminotransferase increased	5 (38.46%)	4 (26.67%)	1 (33.33%)	5 (83.33%)	1 (11.11%)	5 (50.00%)	4 (66.67%)	5 (62.50%)	9 (32.14%)	7 (38.89%)	14 (58.33%)	30 (42.86%)
Blood alkaline phosphatase increased	2 (15.38%)	1 (6.67%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (25.00%)	3 (10.71%)	1 (5.56%)	2 (8.33%)	6 (8.57%)
Blood bilirubin increased	1 (7.69%)	1 (6.67%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (7.14%)	2 (11.11%)	1 (4.17%)	5 (7.14%)

Blood calcium decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Blood chloride decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Blood chloride increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Blood creatinine increased	2 (15.38%)	2 (13.33%)	0 (0.00%)	2 (33.33%)	1 (11.11%)	3 (30.00%)	1 (16.67%)	0 (0.00%)	4 (14.29%)	3 (16.67%)	4 (16.67%)	11 (15.71%)
Blood glucose increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Blood lactate dehydrogenase increased	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.86%)
Blood potassium decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Blood sodium decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)

Electrocardiogram QT prolonged	2 (15.38 %)	2 (13.33 %)	0 (0.00%)	1 (16.67 %)	1 (11.11 %)	1 (10.00 %)	0 (0.00%)	1 (12.50 %)	4 (14.29%)	2 (11.11%)	2 (8.33%)	8 (11. 43%)
Gamma-glutamyltransferase increased	0 (0.00 %)	1 (6.67%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	1 (3.57%)	1 (5.56%)	1 (4.17%)	3 (4.2 9%)
Haematocrit decreased	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (4.17%)	2 (2.8 6%)
Haemoglobin decreased	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Heart rate increased	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Lipase increased	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Lymphocyte count decreased	2 (15.38 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	1 (16.67 %)	1 (12.50 %)	2 (7.14%)	0 (0.00%)	3 (12.50%)	5 (7.1 4%)
Monocyte count increased	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)

Neutrophil count decreased	2 (15.38%)	2 (13.33%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	1 (16.67%)	1 (12.50%)	4 (14.29%)	1 (5.56%)	4 (16.67%)	9 (12.86%)
Platelet count decreased	3 (23.08%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (25.00%)	3 (10.71%)	1 (5.56%)	3 (12.50%)	7 (10.00%)
Protein total decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Transaminases increased	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (25.00%)	1 (3.57%)	0 (0.00%)	3 (12.50%)	4 (5.71%)
Weight decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	1 (11.11%)	1 (10.00%)	3 (50.00%)	1 (12.50%)	0 (0.00%)	3 (16.67%)	5 (20.83%)	8 (11.43%)
Weight increased	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
White blood cell count decreased	4 (30.77%)	2 (13.33%)	1 (33.33%)	0 (0.00%)	1 (11.11%)	2 (20.00%)	1 (16.67%)	2 (25.00%)	6 (21.43%)	2 (11.11%)	5 (20.83%)	13 (18.57%)
Metabolism and nutrition disorders												
Decreased appetite	6 (46.15%)	2 (13.33%)	1 (33.33%)	1 (16.67%)	4 (44.44%)	3 (30.00%)	3 (50.00%)	5 (62.50%)	8 (28.57%)	6 (33.33%)	11 (45.83%)	25 (35.71%)

Dehydration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	2 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	3 (12.50%)	4 (5.71%)
Hypercalcaemia	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (5.56%)	0 (0.00%)	2 (2.86%)
Hypercholesterolaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Hyperglycaemia	2 (15.38%)	0 (0.00%)	2 (66.67%)	5 (83.33%)	5 (55.56%)	4 (40.00%)	1 (16.67%)	4 (50.00%)	2 (7.14%)	12 (66.67%)	9 (37.50%)	23 (32.86%)
Hyperkalaemia	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hypermagnesaemia	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%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Hypernatraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Hypoalbuminaemia	2 (15.38%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	1 (5.56%)	0 (0.00%)	3 (4.29%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (5.56%)	1 (4.17%)	2 (2.86%)
Hypoglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Hypokalaemia	1 (7.69%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	1 (10.00%)	2 (33.33%)	0 (0.00%)	1 (3.57%)	2 (11.11%)	3 (12.50%)	6 (8.57%)
Hypomagnesaemia	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (3.57%)	1 (5.56%)	1 (4.17%)	3 (4.29%)
Hyponatraemia	2 (15.38%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	1 (5.56%)	1 (4.17%)	4 (5.71%)

Hypophosphataemia	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	2 (25.00 %)	0 (0.00%)	0 (0.00%)	3 (12.50%)	3 (4.29%)
Musculoskeletal and connective tissue disorders												
Arthralgia	2 (15.38 %)	4 (26.67 %)	0 (0.00%)	1 (16.67 %)	1 (11.11 %)	2 (20.00 %)	1 (16.67 %)	2 (25.00 %)	6 (21.43%)	2 (11.11%)	5 (20.83%)	13 (18.57 %)
Back pain	1 (7.69 %)	3 (20.00 %)	1 (33.33 %)	0 (0.00%)	0 (0.00%)	2 (20.00 %)	1 (16.67 %)	1 (12.50 %)	4 (14.29%)	1 (5.56%)	4 (16.67%)	9 (12.86%)
Bone pain	1 (7.69 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Joint swelling	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Muscle spasms	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (30.00 %)	0 (0.00%)	1 (12.50 %)	1 (3.57%)	0 (0.00%)	4 (16.67%)	5 (7.14%)
Muscular weakness	0 (0.00 %)	1 (6.67%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (5.56%)	0 (0.00%)	2 (2.86%)
Musculoskeletal chest pain	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (5.56%)	0 (0.00%)	2 (2.86%)
Musculoskeletal pain	2 (15.38 %)	2 (13.33 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (20.00 %)	0 (0.00%)	0 (0.00%)	4 (14.29%)	0 (0.00%)	2 (8.33%)	6 (8.57%)
Myalgia	1 (7.69 %)	2 (13.33 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	3 (10.71%)	0 (0.00%)	1 (4.17%)	4 (5.71%)
Neck pain	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)

Osteonecrosis of jaw	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Pain in extremity	1 (7.69%)	3 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	4 (14.29%)	0 (0.00%)	1 (4.17%)	5 (7.14%)
Pain in jaw	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Scoliosis	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Malignant melanoma	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Nervous system disorders												
Ataxia	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Dizziness	2 (15.38%)	1 (6.67%)	1 (33.33%)	2 (33.33%)	1 (11.11%)	1 (10.00%)	0 (0.00%)	1 (12.50%)	3 (10.71%)	4 (22.22%)	2 (8.33%)	9 (12.86%)
Dysgeusia	2 (15.38%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	3 (37.50%)	2 (7.14%)	0 (0.00%)	5 (20.83%)	7 (10.00%)
Headache	1 (7.69%)	3 (20.00%)	1 (33.33%)	4 (66.67%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (25.00%)	4 (14.29%)	5 (27.78%)	3 (12.50%)	12 (17.14%)

Hyperaesthesia	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hypoaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.86%)
Migraine with aura	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Neuralgia	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.86%)
Neuropathy peripheral	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (5.56%)	0 (0.00%)	2 (2.86%)
Paraesthesia	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Parosmia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Peripheral sensory neuropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Somnolence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (4.17%)	2 (2.86%)
Tremor	0 (0.00%)	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Visual field defect	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Psychiatric disorders												

Anxiety	2 (15.38 %)	1 (6.67%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	2 (20.00 %)	0 (0.00%)	2 (25.00 %)	3 (10.71%)	1 (5.56%)	4 (16.67%)	8 (11. 43%)
Confusi onal state	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Depress ed mood	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Depress ion	1 (7.69 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	1 (16.67 %)	0 (0.00%)	2 (7.14%)	0 (0.00%)	2 (8.33%)	4 (5.7 1%)
Emotion al distress	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Insomni a	0 (0.00 %)	1 (6.67%)	1 (33.33 %)	1 (16.67 %)	3 (33.33 %)	0 (0.00%)	0 (0.00%)	2 (25.00 %)	1 (3.57%)	5 (27.78%)	2 (8.33%)	8 (11. 43%)
Mood altered	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	2 (25.00 %)	0 (0.00%)	0 (0.00%)	3 (12.50%)	3 (4.2 9%)
Mood swings	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.4 3%)
Renal and urinary disorders												
Acute kidney injury	0 (0.00 %)	0 (0.00%)	1 (33.33 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)
Chroma turia	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.4 3%)
Dysuria	1 (7.69 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	1 (4.17%)	3 (4.2 9%)
Nocturia	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.4 3%)
Pollakiu ria	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.4 3%)

Strangury	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Urinary hesitation	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Reproductive system and breast disorders												
Breast pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Vaginal haemorrhage	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Vulvovaginal dryness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Respiratory, thoracic and mediastinal disorders												
Chronic obstructive pulmonary disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Cough	5 (38.46%)	0 (0.00%)	1 (33.33%)	1 (16.67%)	2 (22.22%)	1 (10.00%)	1 (16.67%)	0 (0.00%)	5 (17.86%)	4 (22.22%)	2 (8.33%)	11 (15.71%)

Dysphonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Dyspnoea	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	2 (25.00%)	1 (3.57%)	0 (0.00%)	4 (16.67%)	5 (7.14%)
Dyspnoea exertional	2 (15.38%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (7.14%)	0 (0.00%)	1 (4.17%)	3 (4.29%)
Hypoxia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Interstitial lung disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Nasal congestion	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.86%)
Oropharyngeal pain	1 (7.69%)	1 (6.67%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	1 (5.56%)	0 (0.00%)	3 (4.29%)
Paranasal sinus hypersecretion	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Pneumonitis	2 (15.38%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (7.14%)	0 (0.00%)	1 (4.17%)	3 (4.29%)
Productive cough	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (5.56%)	0 (0.00%)	2 (2.86%)
Respiratory tract congestion	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.86%)
Rhinorrhoea	1 (7.69%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	2 (22.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	2 (11.11%)	0 (0.00%)	4 (5.71%)

Sinus congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Wheezing	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Skin and subcutaneous tissue disorders												
Alopecia	0 (0.00%)	1 (6.67%)	1 (33.33%)	1 (16.67%)	2 (22.22%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (3.57%)	4 (22.22%)	1 (4.17%)	6 (8.57%)
Dermatitis allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Dry skin	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (30.00%)	2 (33.33%)	1 (12.50%)	1 (3.57%)	0 (0.00%)	6 (25.00%)	7 (10.00%)
Eczema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Erythema	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (4.17%)	2 (2.86%)
Madarosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Nail disorder	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%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (1.43%)
Pruritus	4 (30.77%)	4 (26.67%)	0 (0.00%)	1 (16.67%)	1 (11.11%)	2 (20.00%)	3 (50.00%)	3 (37.50%)	8 (28.57%)	2 (11.11%)	8 (33.33%)	18 (25.71%)

Rash	1 (7.69 %)	2 (13.33 %)	1 (33.33 %)	1 (16.67 %)	6 (66.67 %)	5 (50.00 %)	1 (16.67 %)	4 (50.00 %)	3 (10.71%)	8 (44.44%)	10 (41.67 %)	21 (30.00 %)
Rash maculo-papular	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	3 (30.00 %)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	1 (5.56%)	4 (16.67%)	5 (7.14%)
Rash pruritic	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	1 (5.56%)	1 (4.17%)	2 (2.86%)
Skin discolouration	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Skin exfoliation	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (4.17%)	2 (2.86%)
Skin hypopigmentation	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Skin irritation	1 (7.69 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Urticaria	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)
Vitiligo	0 (0.00 %)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Vascular disorders												
Hot flush	1 (7.69 %)	2 (13.33 %)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (10.71%)	1 (5.56%)	0 (0.00%)	4 (5.71%)
Hypotension	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.86%)
Peripheral coldness	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50 %)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.43%)

Other Relevant Findings

RP2D/MTD:

The RP2D for Arm 3 was confirmed at LEE011 600 mg (3 weeks on, 1week off) + fulvestrant. The RP2D for Arm 3A was confirmed at LEE011 400 mg continuous + fulvestrant.

The combination of LEE011 400 mg (3 weeks on, 1 week off) +BKM120 30 mg (daily) + fulvestrant was determined to be the RP2D. Dose escalation in the triplet combinations were stopped due to elevated rates of adverse events considered incompatible with long-term dosing. As a result, the RP2D was not determined for the combination of LEE011 + BYL719 + fulvestrant. The MTD was not declared for any of the arms.

Conclusion:

- LEE011 (Ribociclib) 600 mg (3 weeks on, 1 week off regimen) + fulvestrant 500 mg (dosed on Days 1 and 15 in Cycle 1, and Day 1 of each subsequent cycle) was confirmed as the RP2D in patients with HR-positive/HER2-negative advanced breast cancer.
- LEE011 (Ribociclib) in combination with fulvestrant demonstrated clinical activity in patients with HR-positive/HER2-negative advanced breast cancer who had failed or progressed on AI treatment.
- LEE011 (Ribociclib) 400 mg (3 weeks on, 1 week off regimen) + BKM120 30 mg (daily) + fulvestrant 500 mg was confirmed as the RP2D for this triplet combination in patients with HRpositive/HER2-negative advanced breast cancer.
- Dose escalations in the triplet combinations were stopped due to elevated rates of adverse events considered incompatible with long-term dosing. As a result, the RP2D was not determined for the combination of LEE011 + BYL719 + fulvestrant.
- LEE011 (Ribociclib) in combination with BKM120 plus fulvestrant demonstrated clinical activity in patients with HR-positive/HER2-negative advanced breast cancer who had failed or progressed on AI treatment.
- PK results on Cycle 1 Day 21 following administration of LEE011 (Ribociclib) 400 mg (continuous daily dosing) or 600 mg (3 weeks on, 1 week off regimen) + fulvestrant in combination with BYL719 or BKM120, suggested no marked differences in LEE011 (Ribociclib) PK in the presence of any of the combination partners.

Date of Clinical Trial Report

11March2019