Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ribociclib/LEE011

Trial Indication(s)

Advanced solid tumors or lymphomas

Protocol Number

CLEE011X2101

Protocol Title

A phase1 multi-center, open label, dose-escalation study of oral LEE011 in patients with advanced solid tumors or lymphoma

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1

Study Start/End Dates

Study Start Date: December 2010 (Actual)
Primary Completion Date: March 2017 (Actual)
Study Completion Date: March 2017 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a Phase I, multi-center, open-label dose-escalation study of ribociclib administered orally once daily for either 21 days followed by a 7-day rest period or continuous daily dosing (28-day cycle) in adult subjects with solid tumors or lymphomas that have progressed despite standard therapy and for which no standard therapy was available. Enrollment in this study was restricted to subjects with tumors that had intact retinoblastoma protein (pRb).
The study began with a dose-escalation phase in which successive cohorts of newly enrolled subjects received increasing doses of ribociclib with the initially planned dosing schedule (21 days of daily dosing followed by a 1-week break in a 28-day cycle) until the MTD/RDE was determined. At the time of the MTD declaration for the initially planned dosing schedule, if safety and PK data supported it, evaluation of a continuous dosing regimen was planned to be evaluated to establish an MTD for that regimen. After the MTD was declared for the ribociclib (administered once daily 3 weeks on/1 week off), additional subjects were enrolled and treated before beginning the expansion phase to further define the safety, PK or PD profile of ribociclib for potential RDE levels lower than the determined MTD.
Prior to the declaration of RDE (600 mg administered once daily 3 weeks on/1 week off), the only continuous dosing regimen which was explored was the 600 mg dose level. The 300 and 400 mg continuous dose levels were opened after the declaration of the RDE and only included subjects with estrogen receptor positive (ER+) breast cancer.
The dose expansion phase was conducted at the RDE (600 mg, 3 weeks on/1 week off) to further evaluate safety, tolerability, PK, and PD. The dose expansion phase limited enrollment to subjects with tumor types known to harbor defects in the cyclin D CDK4/6-INK4a-pRb pathway, to select for subjects most likely to respond to ribociclib.

Centers

7 centers in 3 countries: United States(4), Netherlands(1), France(2)

Objectives:

Primary Objective:

- The primary objective was to determine the maximum tolerated doses (MTDs) and/or the recommended dose for expansion (RDE), and to characterize the dose-limiting toxicities (DLT) of ribociclib.

Secondary Objectives:

The secondary objectives were:

- To characterize the safety and tolerability of ribociclib.
- To characterize the pharmacokinetic (PK) profiles of ribociclib, the LEE011 metabolite LEQ803 and any other clinically significant metabolites that may be identified.
- To characterize the relationship between QTc prolongation and exposure to ribociclib and/or any of its relevant metabolites.
- To assess the pharmacodynamic (PD) effects of ribociclib on the D-cyclin-CDK4/6-INK4a-pRb pathway in tumor tissue by comparing pre-treatment and post-treatment biopsies.
- To characterize any antitumor activity that may be associated with ribociclib treatment.

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

The sponsor supplied ribociclib as 10 mg, 50 mg, and 200 mg capsules. Ribociclib was also available in a liquid formulation at 30 mg/mL solution. Ribociclib was administered orally once daily for either 21 days followed by a 7-day rest period or continuous daily dosing (28-day cycle).

Statistical Methods

All data were analyzed by the Sponsor. SAS® version 9.4 was used in all analyses other than Bayesian analyses. For Bayesian modeling, programs were compiled using R (version 2.8.1 or later) and WinBUGS (version 1.4.3) available in the production environment of MODESIM/Global programming and statistical environment II.
An adaptive BLRM guided by the escalation with overdose control principle was used to guide the dose escalation up to the declaration of MTD/RDE. The dose-toxicity relationship in the dose escalation part of the study was described by a 2 parameter

BLRM for the initially planned 3 weeks on-1 week off regimen. At the time of the MTD declaration, as safety and PK data support it, an alternative schedule (continuous dosing) was explored and a new 2-parameter model of the same form of the BLRM was used. After each cohort of patients, the posterior distribution for the model parameters was obtained by updating the prior distribution with the most up-to-date DLT data.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Patients aged ≥18 years with a histologically or cytologically confirmed diagnosis of a solid tumor or lymphoma for which no further effective standard treatment is available
2. Patients must have an ECOG performance status of 0 - 1
3. Patients enrolled in the dose expansion phase must have at least one measurable lesion as defined by RECIST criteria for solid tumors or Measurable nodal disease at baseline as defined by Cheson criteria for Lymphoma.
4. A sufficient interval must have elapsed between the last dose of prior anti-cancer therapy (including cytotoxic and biological therapies and major surgery) and enrollment in this study, to allow the effects of prior therapy to have abated:
- Cytotoxic chemotherapy: ≥ the duration of the cycle of the most recent treatment regimen (a minimum of 2 weeks for all regimens, except 6 weeks for nitrosoureas and mitomycin-C).
- Biologic therapy (e.g., antibodies): ≥ 4 weeks.
5. Patients must have adequate organ function, as defined by the following parameters:
- Bone marrow: Absolute Neutrophil Count (ANC) ≥ 1.5 x 109/L, Hemoglobin (Hgb) ≥ 9 g/dL, Platelets ≥ 100 x 109/L
- Hepatic function: Serum total bilirubin ≤ 1.5 x ULN (upper limit of normal); AST (SGOT) and ALT (SGPT) ≤ 3 x ULN, except in patients with tumor involvement of the liver who must have AST and ALT ≤ 5 x ULN
- Renal function: Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 40 ml/min, Serum potassium, magnesium and calcium must be within normal limits

Exclusion Criteria:

1. Patients with primary central nervous system tumors or brain metastases. However, if radiation therapy and/or surgery has been completed and serial evaluation by CT (with contrast enhancement) or MRI over a minimum of 3 months demonstrates the disease to be stable and if the patient remains asymptomatic, then the patient may be enrolled. Such patients must have no need for treatment with steroids or anti-epileptic medications.
2. Impairment of gastro-intestinal (GI) function or GI disease that may significantly alter the absorption of LEE011 such as patients with a history of GI surgery which may result in intestinal blind loops and patients with clinically significant gastroparesis, unresolved nausea, vomiting, or diarrhea of CTCAE grade > 1
3. Prior hematopoietic stem cell or bone marrow transplantation
4. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
- LVEF <45% as determined by MUGA or echo
- Complete left bundle branch block
- Obligate use of a cardiac pacemaker or implantable cardioverter defibrillator

- Congenital long QT syndrome or family history of unexpected sudden cardiac death
- History or presence of ventricular tachyarrhythmia
- Presence of unstable atrial fibrillation (ventricular response > 100 bpm
- Clinically significant resting bradycardia
- QTcF >450 ms for males and >470 ms for females on screening ECG
- Right bundle branch block and left anterior hemiblock (bifascicular block)
- Angina pectoris ≤ 3 months prior to dosing with study drug
- Acute MI ≤ 3 months prior to dosing with study drug
- Other clinically significant heart disease

5. Acute myocardial infarction or angina pectoris ≤ 3 months prior to starting study drug
6. Patients with concurrent severe and/or uncontrolled concurrent medical conditions that could compromise participation in the study (e.g. uncontrolled hypertension and/or diabetes mellitus, clinically significant pulmonary disease, clinically significant neurological disorder, active or uncontrolled infection). Known diagnosis of HIV or hepatitis C

Participant Flow Table

Table 1

	LEE011 < 400mg N=23 n (%)	LEE011 400 mg N=5 n (%)	LEE011 600 mg N=68 n (%)	LEE011 600 mg liquid form. N=8 n (%)	LEE011 Pooled 600 mg N=76 n (%)	LEE011 > 600mg N=30 n (%)	All subjects 3wk on/ 1 wk off N=134 n (%)	LEE011 300 mg 28d cont. N=6 n (%)	LEE011 400 mg 28d cont. N=6 n (%)	LEE011 600 mg 28d cont. N=7 n (%)	All subjects 28d cont. N=19 n (%)
Subjects treated											
Treatment discontinued	23 (100)	5 (100)	68 (100)	8 (100)	76 (100)	30 (100)	134 (100)	6 (100)	6 (100)	7 (100)	19 (100)
Primary reason for end of treatment											

	LEE011 < 400mg N=23 n (%)	LEE011 400 mg N=5 n (%)	LEE011 600 mg N=68 n (%)	LEE011 600 mg liquid form. N=8 n (%)	LEE011 Pooled 600 mg N=76 n (%)	LEE011 > 600mg N=30 n (%)	All subjects 3wk on/ 1 wk off N=134 n (%)	LEE011 300 mg 28d cont. N=6 n (%)	LEE011 400 mg 28d cont. N=6 n (%)	LEE011 600 mg 28d cont. N=7 n (%)	All subjects 28d cont. N=19 n (%)
Adverse Event(s)	2 (8.7)	0	7 (10.3)	0	7 (9.2)	2 (6.7)	11 (8.2)	1 (16.7)	1 (16.7)	0	2 (10.5)
Abnormal test procedure result(s)	0	0	0	0	0	1 (3.3)	1 (0.7)	0	0	0	0
Subject withdrew consent	1 (4.3)	0	2 (2.9)	0	2 (2.6)	1 (3.3)	4 (3.0)	1 (16.7)	0	0	1 (5.3)
Lost to follow-up	0	0	1 (1.5)	0	1 (1.3)	0	1 (0.7)	0	0	0	0
Death	0	1 (20.0)	0	0	0	0	1 (0.7)	0	0	0	0
Disease progression	20 (87.0)	4 (80.0)	58 (85.3)	7 (87.5)	65 (85.5)	26 (86.7)	115 (85.8)	4 (66.7)	5 (83.3)	7 (100)	16 (84.2)
Missing	0	0	0	1 (12.5)	1 (1.3)	0	1 (0.7)	0	0	0	0
Study evaluation after completion of treatment											
Subjects no longer being followed for study evaluation completion	23 (100)	5 (100)	68 (100)	8 (100)	76 (100)	30 (100)	134 (100)	6 (100)	6 (100)	7 (100)	19 (100)
Primary reason for study evaluation											

	LEE011 < 400mg N=23 n (%)	LEE011 400 mg N=5 n (%)	LEE011 600 mg N=68 n (%)	LEE011 600 mg liquid form. N=8 n (%)	LEE011 Pooled 600 mg N=76 n (%)	LEE011 > 600mg N=30 n (%)	All subjects 3wk on/ 1 wk off N=134 n (%)	LEE011 300 mg 28d cont. N=6 n (%)	LEE011 400 mg 28d cont. N=6 n (%)	LEE011 600 mg 28d cont. N=7 n (%)	All subjects 28d cont. N=19 n (%)
completion											
Subject withdrew consent	3 (13.0)	0	1 (1.5)	0	1 (1.3)	1 (3.3)	5 (3.7)	1 (16.7)	0	0	1 (5.3)
Lost to follow-up	1 (4.3)	0	13 (19.1)	0	13 (17.1)	1 (3.3)	15 (11.2)	0	0	1 (14.3)	1 (5.3)
Death	3 (13.0)	1 (20.0)	7 (10.3)	1 (12.5)	8 (10.5)	6 (20.0)	18 (13.4)	0	0	1 (14.3)	1 (5.3)
Disease progression	0	0	1 (1.5)	0	1 (1.3)	1 (3.3)	2 (1.5)	0	0	0	0
Protocol deviation	0	0	1 (1.5)	0	1 (1.3)	0	1 (0.7)	0	0	0	0
F/u phase completed as per protocol	16 (69.6)	4 (80.0)	45 (66.2)	7 (87.5)	52 (68.4)	21 (70.0)	93 (69.4)	5 (83.3)	6 (100)	5 (71.4)	16 (84.2)

- * Subjects ongoing at the time of the cut-off 26APR2017
- Study evaluation completion corresponds to the evaluation performed 28-day following treatment discontinuation.

Baseline Characteristics

Table 2

Demographics variables	LEE011 < 400mg N=23	LEE011 400 mg N=5	LEE011 600 mg N=68	LEE011 600 mg liquid form. N=8	LEE011 Pooled 600 mg N=76	LEE011 > 600mg N=30	All subjects 3wk on/ 1 wk off N=134
Age (Years, at screening)							
n	23	5	68	8	76	30	134
Mean (SD)	59.0 (11.25)	54.8 (13.37)	58.7 (11.48)	57.1 (11.87)	58.5 (11.45)	59.0 (10.81)	58.6 (11.24)
Median	61.0	52.0	60.5	52.0	60.0	60.0	60.0
Min-Max	26 - 76	39 - 70	22 - 84	43 - 76	22 - 84	31 - 76	22 - 84
Age category (Years, at screening) -n (%)							
<40	1 (4.3)	1 (20.0)	3 (4.4)	0	3 (3.9)	1 (3.3)	6 (4.5)
40-<50	3 (13.0)	1 (20.0)	10 (14.7)	2 (25.0)	12 (15.8)	6 (20.0)	22 (16.4)
50-<60	6 (26.1)	1 (20.0)	19 (27.9)	3 (37.5)	22 (28.9)	8 (26.7)	37 (27.6)
60-<70	10 (43.5)	1 (20.0)	26 (38.2)	2 (25.0)	28 (36.8)	9 (30.0)	48 (35.8)
>=70	3 (13.0)	1 (20.0)	10 (14.7)	1 (12.5)	11 (14.5)	6 (20.0)	21 (15.7)
Sex -n (%)							
Male	13 (56.5)	3 (60.0)	25 (36.8)	0	25 (32.9)	21 (70.0)	62 (46.3)
Female	10 (43.5)	2 (40.0)	43 (63.2)	8 (100)	51 (67.1)	9 (30.0)	72 (53.7)
Predominant race -n (%)							
Caucasian	18 (78.3)	4 (80.0)	58 (85.3)	8 (100)	66 (86.8)	20 (66.7)	108 (80.6)
Black	0	0	5 (7.4)	0	5 (6.6)	2 (6.7)	7 (5.2)
Asian	0	0	2 (2.9)	0	2 (2.6)	0	2 (1.5)
Other	0	0	0	0	0	1 (3.3)	1 (0.7)

Demographics variables	LEE011 < 400mg N=23	LEE011 400 mg N=5	LEE011 600 mg N=68	LEE011 600 mg liquid form. N=8	LEE011 Pooled 600 mg N=76	LEE011 > 600mg N=30	All subjects 3wk on/ 1 wk off N=134
Missing	5 (21.7)	1 (20.0)	3 (4.4)	0	3 (3.9)	7 (23.3)	16 (11.9)
Ethnicity -n (%)							
Hispanic/Latino	0	0	1 (1.5)	0	1 (1.3)	0	1 (0.7)
Other	18 (78.3)	4 (80.0)	57 (83.8)	8 (100)	65 (85.5)	23 (76.7)	110 (82.1)
Missing	5 (21.7)	1 (20.0)	10 (14.7)	0	10 (13.2)	7 (23.3)	23 (17.2)
Weight (kg, at baseline)							
n	23	5	68	8	76	30	134
Mean (SD)	78.9 (14.76)	77.8 (9.71)	75.0 (20.81)	74.7 (25.34)	74.9 (21.14)	79.1 (14.19)	76.6 (18.40)
Median	79.6	75.0	72.4	71.5	72.3	80.0	74.7
Min-Max	50 - 112	69 - 94	34 - 159	50 - 124	34 - 159	52 - 111	34 - 159
Weight category(Kg) -n (%)							
<55	2 (8.7)	0	11 (16.2)	2 (25.0)	13 (17.1)	1 (3.3)	16 (11.9)
55-<75	7 (30.4)	3 (60.0)	28 (41.2)	4 (50.0)	32 (42.1)	12 (40.0)	54 (40.3)
>=75	14 (60.9)	2 (40.0)	29 (42.6)	2 (25.0)	31 (40.8)	17 (56.7)	64 (47.8)
Height (cm, at screening)							
n	23	5	68	8	76	30	134
Mean (SD)	170.9 (10.04)	171.8 (11.46)	168.1 (9.34)	163.4 (4.79)	167.6 (9.06)	175.7 (8.04)	170.1 (9.58)
Median	171.0	176.0	168.0	163.1	167.0	175.0	170.2
Min-Max	147 - 186	152 - 182	143 - 187	158 - 173	143 - 187	155 - 192	143 - 192
Body mass index (kg/m2)							
n	23	5	68	8	76	30	134

Demographics variables	LEE011 < 400mg N=23	LEE011 400 mg N=5	LEE011 600 mg N=68	LEE011 600 mg liquid form. N=8	LEE011 Pooled 600 mg N=76	LEE011 > 600mg N=30	All subjects 3wk on/ 1 wk off N=134
Mean (SD)	27.1 (5.26)	26.5 (3.78)	26.3 (5.93)	27.8 (8.43)	26.4 (6.19)	25.5 (3.25)	26.3 (5.40)
Median	26.8	25.5	25.1	26.1	25.4	25.9	25.8
Min-Max	17 - 39	23 - 31	17 - 46	19 - 42	17 - 46	20 - 33	17 - 46
Body mass index category (kg/ m2) -n (%)							
<30	18 (78.3)	3 (60.0)	56 (82.4)	6 (75.0)	62 (81.6)	27 (90.0)	110 (82.1)
>=30	5 (21.7)	2 (40.0)	12 (17.6)	2 (25.0)	14 (18.4)	3 (10.0)	24 (17.9)
WHO/ECOG performance status ($) -n (%)							
0	7 (30.4)	2 (40.0)	27 (39.7)	4 (50.0)	31 (40.8)	7 (23.3)	47 (35.1)
1	16 (69.6)	3 (60.0)	41 (60.3)	4 (50.0)	45 (59.2)	23 (76.7)	87 (64.9)

- Body Mass Index: $BMI_{kg/m2} = weight_{kg, at\ baseline} / (height_{m, at\ screening}$ **2)
- ($) 0 - Fully active, able to carry on all pre-disease performance without restriction;
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work;

Summary of Efficacy

.

Primary Outcome Result(s)

Table 3 Dose limiting toxicities starting during the first 28 days of treatment by primary system organ class, preferred term, and treatment (Dose determining set)

	Ribociclib						
Primary system organ class **Preferred term**	**<400 mg N=22** **n (%)**	**400 mg N=4** **n (%)**	**600 mg N=64** **n (%)**	**600 mg liquid N=8** **n (%)**	**Pooled 600 mg N=72** **n (%)**	**>600 mg N=28** **n (%)**	**All Patients[1] N=126** **n (%)**
Any primary system organ class	**2 (9.1)**	**1 (25.0)**	**5 (7.8)**	**1 (12.5)**	**6 (8.3)**	**5 (17.9)**	**14 (11.1)**
Blood And Lymphatic System Disorders	**0**	**1 (25.0)**	**4 (6.3)**	**0**	**4 (5.6)**	**4 (14.3)**	**9 (7.1)**
Thrombocytopenia	0	0	1 (1.6)	0	1 (1.4)	3 (10.7)	4 (3.2)
Neutropenia	0	1 (25.0)	2 (3.1)	0	2 (2.8)	0	3 (2.4)
Febrile Neutropenia	0	0	1 (1.6)	0	1 (1.4)	1 (3.6)	2 (1.6)
Investigations	**0**	**0**	**1 (1.6)**	**1 (12.5)**	**2 (2.8)**	**1 (3.6)**	**3 (2.4)**
Electrocardiogram QT Prolonged	0	0	0	1 (12.5)	1 (1.4)	1 (3.6)	2 (1.6)
Platelet Count Decreased	0	0	1 (1.6)	0	1 (1.4)	0	1 (0.8)
Gastrointestinal Disorders	**1 (4.5)**	**0**	**0**	**0**	**0**	**0**	**1 (0.8)**
Stomatitis	1 (4.5)	0	0	0	0	0	1 (0.8)
Infections And Infestations	**1 (4.5)**	**0**	**0**	**0**	**0**	**0**	**1 (0.8)**
Herpes Simplex	1 (4.5)	0	0	0	0	0	1 (0.8)
Respiratory, Thoracic And Mediastinal Disorders	**1 (4.5)**	**0**	**0**	**0**	**0**	**0**	**1 (0.8)**
Pulmonary Embolism	1 (4.5)	0	0	0	0	0	1 (0.8)

[1] 3 weeks on/1 week off

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the <all patients> column
A patient with multiple occurrences of an DLTs under one treatment is counted only once in the AE category for that treatment.
A patient with multiple DLTs within a primary system organ class is counted only once in the total row.

Table 4 Summary of posterior distribution of DLT rates at the RDE declaration (Dose determining set)

	3 weeks on, 1 week off capsule							
	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
Dose level (mg)	Under-dosing 0-0.16	Targeted toxicity 0.16-0.33	Excessive toxicity 0.33-1	Mean	SD	2.5%	50%	97.5%
50	0.990	0.010	0.000	0.052	0.036	0.005	0.044	0.140
70	0.986	0.014	0.000	0.059	0.037	0.008	0.052	0.146
140	0.971	0.029	0.000	0.077	0.038	0.018	0.072	0.164
260	0.924	0.076	0.000	0.101	0.039	0.037	0.096	0.188
280	0.915	0.085	0.000	0.104	0.039	0.040	0.100	0.192
350	0.869	0.131	0.000	0.115	0.040	0.049	0.111	0.203
400	0.829	0.171	0.000	0.122	0.040	0.055	0.118	0.211
600	0.634	0.365	0.000	0.148	0.046	0.070	0.144	0.247
750	0.501	0.495	0.003	0.164	0.051	0.077	0.160	0.278
900	0.399	0.588	0.012	0.179	0.058	0.083	0.174	0.306
1200	0.282	0.663	0.055	0.205	0.072	0.089	0.197	0.366

Secondary Outcome Result(s)

Table 5 Summary of best overall response per RECIST and CHESON as per investigator assessment by regimen and treatment

	LEE011 < 400 mg (N=23) n (%)	LEE011 400 mg (N=5) n (%)	LEE011 600 mg caps. (N=68) n (%)	LEE011 600 mg liquid form. (N=8) n (%)	> 600 mg (N=30) n (%)	All subjects@ 3 wks on/1 wk off (N=134) n (%)	LEE011 @300mg @cont. (N=6)	LEE011 @400mg @cont. (N=6)	LEE011 @600mg @cont. (N=7)	All subjects @ cont. (N=19)
Best overall response										
Complete Response (CR)	0	0	0	0	0	0	0	0	0	0
Partial Response (PR)	0	0	4 (5.9)	0	0	4 (3.0)	0	0	1(14.3)	1(5.3)
Stable Disease (SD)	7 (30.4)	3 (60.0)	21 (30.9)	2 (25.0)	14 (46.7)	47 (35.1)	5(83.3)	4 (66.7)	4(57.1)	13(68.4)
Progressive Disease (PD)	12 (52.2)	0	37 (54.4)	3 (37.5)	13 (43.3)	65 (48.5)	1(16.7)	2(33.3)	1(14.3)	4(21.1)
Unknown	4 (17.4)	2 (40.0)	6 (8.8)	3 (37.5)	3 (10.0)	18 (13.4)	0	0	1(14.3)	1(5.3)
Overall response rate (CR or PR)	0	0	4 (5.9)	0	0	4 (3.0)	0	0	1(14.3)	1(5.3)
90 % Confidence interval	[0.0; 12.2]	[0.0; 45.1]	[2.0; 13.0]	[0.0; 31.2]	[0.0; 9.5]	[1.0; 6.7]	[0.0; 39.3]	[0.0; 39.3]	[0.7; 52.1]	[0.3; 22.6]

	LEE011 < 400 mg (N=23) n (%)	LEE011 400 mg (N=5) n (%)	LEE011 600 mg caps. (N=68) n (%)	LEE011 600 mg liquid form. (N=8) n (%)	> 600 mg (N=30) n (%)	All subjects@ 3 wks on/1 wk off (N=134) n (%)	LEE011 @300mg @cont. (N=6)	LEE011 @400mg @cont. (N=6)	LEE011 @600mg @cont. (N=7)	All subjects @ cont. (N=19)
Disease control rate (CR or PR or SD)	7 (30.4)	3 (60.0)	25 (36.8)	2 (25.0)	14 (46.7)	51 (38.1)	5 (83.3)	4(66.7)	5(71.4)	14 (73.7)
90 % Confidence interval	[15.2; 49.6]	[18.9; 92.4]	[27.0; 47.4]	[4.6; 60.0]	[30.8; 63.0]	[31.0; 45.5]	[41.8; 99.1]	[21.7; 93.7]	[34.1; 94.7]	[52.4; 89.0]

Table 6 **Adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class, preferred term and treatment group (with at least a 5% incidence – All subjects 28 d cont.) (Safety analysis set)**

Primary system organ class Preferred term	All subjects 3 wk on/ 1 wk off N = 134 n (%)	LEE011 300 mg 28 d cont. N = 6 n (%)	LEE011 400 mg 28 d cont. N = 6 n (%)	LEE011 600 mg 28 d cont. N = 7 n (%)	All subjects 28 d cont. N = 19 n (%)
-Any primary system organ class					
-Total	11 (8.2)	1 (16.7)	1 (16.7)	0	2 (10.5)
Investigations					
-Total	1 (0.7)	1 (16.7)	1 (16.7)	0	2 (10.5)
Alanine Aminotransferase Increased	0	0	1 (16.7)	0	1 (5.3)
Aspartate Aminotransferase Increased	0	0	1 (16.7)	0	1 (5.3)

Primary system organ class Preferred term	All subjects 3 wk on/ 1 wk off N = 134 n (%)	LEE011 300 mg 28 d cont. N = 6 n (%)	LEE011 400 mg 28 d cont. N = 6 n (%)	LEE011 600 mg 28 d cont. N = 7 n (%)	All subjects 28 d cont. N = 19 n (%)
Electrocardiogram QT Prolonged	0	1 (16.7)	0	0	1 (5.3)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alpha betically.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A subject with multiple adverse events within a primary system organ class is counted only once in the total row.
- Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Table 7 All grades and Grade 3/4 adverse events, regardless of study drug relationship, by preferred term, regimen and treatment (with at least a 20% incidence - All subjects 28 d cont. /All grade) (Safety set)

	All subjects 3 wk on/ 1 wk off N = 134		LEE011 300 mg 28 d cont. N = 6		LEE011 400 mg 28 d cont. N = 6		LEE011 600 mg 28 d cont. N = 7		All subjects 28 d cont. N = 19	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	134 (100)	98 (73.1)	5 (83.3)	2 (33.3)	6 (100)	4 (66.7)	7 (100)	7 (100)	18 (94.7)	13 (68.4)
Nausea	70 (52.2)	4 (3.0)	5 (83.3)	0	4 (66.7)	0	3 (42.9)	1 (14.3)	12 (63.2)	1 (5.3)
Fatigue	57 (42.5)	2 (1.5)	1 (16.7)	0	3 (50.0)	0	4 (57.1)	0	8 (42.1)	0
Diarrhoea	50 (37.3)	3 (2.2)	1 (16.7)	0	4 (66.7)	0	1 (14.3)	0	6 (31.6)	0
Vomiting	48 (35.8)	2 (1.5)	0	0	1 (16.7)	0	3 (42.9)	0	4 (21.1)	0
Neutropenia	47 (35.1)	31 (23.1)	3 (50.0)	2 (33.3)	2 (33.3)	2 (33.3)	3 (42.9)	2 (28.6)	8 (42.1)	6 (31.6)
Anaemia	45 (33.6)	5 (3.7)	2 (33.3)	0	1 (16.7)	0	2 (28.6)	0	5 (26.3)	0

	All subjects 3 wk on/ 1 wk off N = 134		LEE011 300 mg 28 d cont. N = 6		LEE011 400 mg 28 d cont. N = 6		LEE011 600 mg 28 d cont. N = 7		All subjects 28 d cont. N = 19	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
White Blood Cell Count Decreased	32 (23.9)	14 (10.4)	3 (50.0)	2 (33.3)	0	0	3 (42.9)	3 (42.9)	6 (31.6)	5 (26.3)
Decreased Appetite	31 (23.1)	3 (2.2)	2 (33.3)	0	0	0	2 (28.6)	1 (14.3)	4 (21.1)	1 (5.3)
Constipation	30 (22.4)	0	1 (16.7)	0	2 (33.3)	0	1 (14.3)	0	4 (21.1)	0
Asthenia	26 (19.4)	4 (3.0)	2 (33.3)	0	0	0	2 (28.6)	1 (14.3)	4 (21.1)	1 (5.3)
Cough	25 (18.7)	1 (0.7)	1 (16.7)	0	2 (33.3)	0	1 (14.3)	0	4 (21.1)	0
Hyperglycaemia	23 (17.2)	0	0	0	1 (16.7)	0	4 (57.1)	0	5 (26.3)	0
Aspartate Aminotransferase Increased	21 (15.7)	7 (5.2)	2 (33.3)	0	1 (16.7)	0	1 (14.3)	0	4 (21.1)	0
Blood Creatinine Increased	21 (15.7)	1 (0.7)	2 (33.3)	0	2 (33.3)	0	1 (14.3)	0	5 (26.3)	0
Abdominal Pain	20 (14.9)	2 (1.5)	2 (33.3)	0	1 (16.7)	0	3 (42.9)	0	6 (31.6)	0
Alanine Aminotransferase Increased	17 (12.7)	3 (2.2)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	1 (14.3)	0	4 (21.1)	2 (10.5)

- Preferred terms are sorted in descending frequency of all grades column, as reported in the All subjects treatment group.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A subject with multiple adverse events is counted only once in the total row.
- Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Table 8 **All grades and Grade 3/4 adverse events, suspected to be study drug related, by preferred term and treatment group (with at least a 20% incidence – All subjects 28 d cont. /All grade) (Safety set)**

	All subjects 3 wk on/ 1 wk off N = 134		LEE011 300 mg 28 d cont. N = 6		LEE011 400 mg 28 d cont. N = 6		LEE011 600 mg 28 d cont. N = 7		All subjects 28 d cont. N = 19	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
-Total	129 (96.3)	71 (53.0)	5 (83.3)	2 (33.3)	6 (100)	4 (66.7)	7 (100)	6 (85.7)	18 (94.7)	12 (63.2)
Nausea	60 (44.8)	2 (1.5)	4 (66.7)	0	4 (66.7)	0	3 (42.9)	0	11 (57.9)	0
Neutropenia	46 (34.3)	31 (23.1)	3 (50.0)	2 (33.3)	2 (33.3)	2 (33.3)	3 (42.9)	2 (28.6)	8 (42.1)	6 (31.6)
Fatigue	45 (33.6)	0	1 (16.7)	0	3 (50.0)	0	4 (57.1)	0	8 (42.1)	0
Anaemia	31 (23.1)	5 (3.7)	2 (33.3)	0	1 (16.7)	0	1 (14.3)	0	4 (21.1)	0
White Blood Cell Count Decreased	30 (22.4)	13 (9.7)	3 (50.0)	2 (33.3)	0	0	3 (42.9)	3 (42.9)	6 (31.6)	5 (26.3)
Asthenia	22 (16.4)	2 (1.5)	2 (33.3)	0	0	0	2 (28.6)	1 (14.3)	4 (21.1)	1 (5.3)
Blood Creatinine Increased	13 (9.7)	0	2 (33.3)	0	2 (33.3)	0	1 (14.3)	0	5 (26.3)	0
Aspartate Aminotransferase Increased	10 (7.5)	2 (1.5)	2 (33.3)	0	1 (16.7)	0	1 (14.3)	0	4 (21.1)	0

- Preferred terms are sorted in descending frequency of all grades column, as reported in the All subjects treatment group.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A subject with multiple adverse events is counted only once in the total row.
- Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Table Error! No text of specified style in document.**-9 Serious adverse events, regardless of study drug relationship, by primary system organ class, preferred term, maximum grade and treatment group (grade 3/4 with an incidence of at least 5% - All subjects 28 d cont.) (Safety analysis set)**

Primary system organ class Preferred term Maximum Grade	All subjects 3 wk on/ 1 wk off N = 134 n (%)	LEE011 300 mg 28 d cont. N = 6 n (%)	LEE011 400 mg 28 d cont. N = 6 n (%)	LEE011 600 mg 28 d cont. N = 7 n (%)	All subjects 28 d cont. N = 19 n (%)
-Any primary system organ class					
-Total	49 (36.6)	0	2 (33.3)	3 (42.9)	5 (26.3)
Grade 3	39 (29.1)	0	1 (16.7)	3 (42.9)	4 (21.1)
Grade 4	8 (6.0)	0	1 (16.7)	0	1 (5.3)
Blood And Lymphatic System Disorders					
-Total	5 (3.7)	0	1 (16.7)	1 (14.3)	2 (10.5)
Grade 3	2 (1.5)	0	0	1 (14.3)	1 (5.3)
Grade 4	3 (2.2)	0	1 (16.7)	0	1 (5.3)
Febrile Neutropenia					
Grade 3	1 (0.7)	0	0	1 (14.3)	1 (5.3)
Neutropenia					
Grade 4	0	0	1 (16.7)	0	1 (5.3)
Gastrointestinal Disorders					
Grade 3	8 (6.0)	0	1 (16.7)	1 (14.3)	2 (10.5)
Nausea					
Grade 3	2 (1.5)	0	0	1 (14.3)	1 (5.3)
Pancreatitis					
Grade 3	0	0	1 (16.7)	0	1 (5.3)
Infections And Infestations					

Primary system organ class Preferred term Maximum Grade	All subjects 3 wk on/ 1 wk off N = 134 n (%)	LEE011 300 mg 28 d cont. N = 6 n (%)	LEE011 400 mg 28 d cont. N = 6 n (%)	LEE011 600 mg 28 d cont. N = 7 n (%)	All subjects 28 d cont. N = 19 n (%)
Grade 3	10 (7.5)	0	1 (16.7)	0	1 (5.3)
Influenza					
Grade 3	1 (0.7)	0	1 (16.7)	0	1 (5.3)
Respiratory, Thoracic And Mediastinal Disorders					
Grade 3	7 (5.2)	0	0	1 (14.3)	1 (5.3)
Dyspnoea					
Grade 3	5 (3.7)	0	0	1 (14.3)	1 (5.3)
Pleural Effusion					
Grade 3	0	0	0	1 (14.3)	1 (5.3)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system Organ class alphabetically.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A subject with multiple grade ratings for an AE while on a treatment, is only counted under the maximum rating.
- Includes all adverse events on study and up to 28 days after last dose.

Table 10 Duration of exposure to study drug, by regimen and treatment (Safety set)

	All subjects 3 wk on/ 1 wk off N = 134	LEE011 300 mg 28 d cont. N = 6	LEE011 400 mg 28 d cont. N = 6	LEE011 600 mg 28 d cont. N = 7	All subjects 28 d cont. N = 19
Exposure categories (cycles) -n (%)					
≤ 1	69 (51.5)	3 (50.0)	2 (33.3)	2 (28.6)	7 (36.8)
2 - ≤ 3	34 (25.4)	0	1 (16.7)	2 (28.6)	3 (15.8)
4 - ≤ 5	9 (6.7)	1 (16.7)	2 (33.3)	1 (14.3)	4 (21.1)
≥ 6	22 (16.4)	2 (33.3)	1 (16.7)	2 (28.6)	5 (26.3)
Exposure categories (days) –n (%)					
≤ 56	77 (57.5)	2 (33.3)	1 (16.7)	3 (42.9)	6 (31.6)
57 - ≤ 84	12 (9.0)	0	1 (16.7)	0	1 (5.3)
85 - ≤ 140	15 (11.2)	1 (16.7)	2 (33.3)	1 (14.3)	4 (21.1)
≥ 141	30 (22.4)	3 (50.0)	2 (33.3)	3 (42.9)	8 (42.1)
Duration of exposure (cycles)					
Mean (standard deviation)	3.9 (7.00)	3.5 (3.83)	3.7 (3.39)	8.0 (10.23)	5.2 (6.85)
Median	1.0	2.5	3.0	3.0	3.0
Min-Max	0 - 39	0 - 9	1 - 10	0 - 26	0 - 26
Duration of exposure (days)					
Mean (standard deviation)	145.5 (218.79)	134.3 (91.28)	133.3 (84.95)	249.9 (293.18)	176.6 (190.46)
Median	52.0	129.5	111.5	119.0	112.0
Minimum-Maximum	4 - 1092	34 - 251	56 - 287	20 - 721	20 - 721

- A subject is counted in only duration range, per treatment.
- Duration of exposure (days) = date of last administration – date of first administration of the study drug + 1.
- Duration of exposure (cycles) = Consider the subject exposed to the drug for one cycle if he/she takes the full dose of the drug for at least 16 days out of the 21 planned days within the cycle (for continuous dosing, at least 21 days out of the 28 planned days).

Table 11 Notably abnormal vital signs by treatment (Safety analysis set)

	Ribociclib						
	<400 mg N=23 All	400 mg N=5 All	600 mg N=68 All	600 mg liquid N=8 All	Pooled 600 mg N=76 All	>600 mg N=30 All	All Patients[1] N=134 All
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Systolic blood pressure (mmHg)							
N*	23 (100)	5 (100)	68 (100)	8 (100)	76 (100)	30 (100)	134 (100)
High only	0	0	4 (5.9)	0	4 (5.3)	1 (3.3)	5 (3.7)
Diastolic blood pressure (mmHg)							
N*	23 (100)	5 (100)	68 (100)	8 (100)	76 (100)	30 (100)	134 (100)
High only	1 (4.3)	0	2 (2.9)	0	2 (2.6)	1 (3.3)	4 (3.0)
Pulse rate (bpm)							
N*	23 (100)	5 (100)	68 (100)	8 (100)	76 (100)	30 (100)	134 (100)
High only	0	0	3 (4.4)	0	3 (3.9)	1 (3.3)	4 (3.0)
Weight (kg)							
N*	23 (100)	5 (100)	68 (100)	8 (100)	76 (100)	30 (100)	134 (100)
Low only	2 (8.7)	0	7 (10.3)	1 (12.5)	8 (10.5)	2 (6.7)	12 (9.0)
High only	0	0	5 (7.4)	0	5 (6.6)	4 (13.3)	9 (6.7)
High and Low	0	0	1 (1.5)	0	1 (1.3)	0	1 (0.7)
Oral body Temperature (°C)							
N*	23 (100)	5 (100)	68 (100)	8 (100)	76 (100)	30 (100)	134 (100)
High only	0	0	0	0	0	1 (3.3)	1 (0.7)
Respiratory rate (bpm)							
N*	23 (100)	5 (100)	68 (100)	8 (100)	76 (100)	30 (100)	134 (100)
Low only	1 (4.3)	0	1 (1.5)	0	1 (1.3)	0	2 (1.5)

[1] 3 weeks on/1 week off

Notably abnormal vital signs: Systolic blood pressure: ≥ 180 mmhg/≤ 90 mmhg with increase/decrease from baseline of ≥ 20 mmhg;
Diastolic blood pressure: ≥ 105 mmhg/≤ 50mmhg with increase/decrease from baseline of ≥ 15 mmhg; Pulse rate: ≥ 120 bpm/≤ 50 bpm with increase/decrease from baseline of ≥ 15 bpm; Weight: ≥ 10 % increase/decrease from baseline; Oral body Temperature: >39°C / ≤35°C; Respiratory rate: ≥ 30 bpm /≤ 10 bpm

If a patient has both High and Low post baseline values then count in High and Low

N* is the total number of patients with baseline and post baseline values, which is used to calculate the percentage

Table Error! No text of specified style in document. **Number (%) of patients with notable ECGs by treatment group for dose escalation patients with non-extensive ECG evaluation schedule (Safety analysis set)**

	Ribociclib				
	<400 mg N=23 Total n (%)	**400 mg N=5 Total n (%)**	**600 mg N=68 Total n (%)**	**>600 mg N=30 Total n (%)**	**All Patients[1] N=134 Total n (%)**
QTcF (msec)					
New ≥ 450	23 (6, 26.1)	5 (2, 40.0)	18 (8, 44.4)	28 (17, 60.7)	74 (33, 44.6)
New >480	23 (0)	5 (0)	20 (3, 15.0)	30 (9, 30.0)	78 (12, 15.4)
New >500	23 (0)	5 (0)	20 (0)	30 (2, 6.7)	78 (2, 2.6)
Increase from baseline >30	23 (10, 43.5)	5 (2, 40.0)	20 (12, 60.0)	30 (24, 80.0)	78 (48, 61.5)
Increase from baseline >60	23 (0)	5 (0)	20 (2, 10.0)	30 (7, 23.3)	78 (9, 11.5)
QTcB (msec)					
New ≥ 450	20 (7, 35.0)	5 (4, 80.0)	17 (12, 70.6)	24 (23, 95.8)	66 (46, 69.7)
New >480	23 (3, 13.0)	5 (0)	20 (5, 25.0)	30 (15, 50.0)	78 (23, 29.5)
New >500	23 (2, 8.7)	5 (0)	20 (1, 5.0)	30 (6, 20.0)	78 (9, 11.5)
Increase from baseline >30	23 (10, 43.5)	5 (3, 60.0)	20 (12, 60.0)	30 (24, 80.0)	78 (49, 62.8)
Increase from baseline >60	23 (1, 4.3)	5 (0)	20 (3, 15.0)	30 (9, 30.0)	78 (13,16.7)
QT (msec)					
New ≥ 450	23 (5, 21.7)	5 (1, 20.0)	19 (6, 31.6)	29 (12, 41.4)	76 (24, 31.6)
New >480	23 (0)	5 (0)	19 (3, 15.8)	30 (6, 20.0)	77 (9, 11.7)
New >500	23 (0)	5 (0)	20 (2, 10.0)	30 (3, 10.0)	78 (5, 6.4)
Increase from baseline >30	23 (14, 60.9)	5 (3, 60.0)	20 (17, 85.0	30 (28, 93.3)	78 (62, 79.5)
Increase from baseline >60	23 (4, 17.4)	5 (1, 20.0)	20 (9, 45.0)	30 (11, 36.7)	78 (25, 32.1)
VR (bpm)					
Mean RR decrease >25% & to a value >100	23 (3, 13.0)	5 (0)	20 (0)	30 (2, 6.7)	78 (5,6.4)
Mean RR increase >25% & to a value <50	23 (3, 13.0)	5 (0)	20 (2, 10.0)	30 (2, 6.7)	78 (7, 9.0)

	Ribociclib				
	<400 mg N=23 Total n (%)	**400 mg N=5 Total n (%)**	**600 mg N=68 Total n (%)**	**>600 mg N=30 Total n (%)**	**All Patients[1] N=134 Total n (%)**
PR (msec)					
Increase from baseline >25% & to a value >200	22 (0)	5 (0)	20 (0)	29 (1, 3.4)	76 (1, 1.3)
QRS (msec)					
Increase from baseline >25% & to a value >110	23 (0)	5 (0)	20 (0)	30 (0)	78 (0)

[1] 3 weeks on/1 week off

New = Newly occurring post baseline value not present at baseline.
Total = number of patients at risk for a specific category. For new abnormality post baseline, this is the number of patients with both baseline and post baseline evaluations, with baseline not meeting the criteria. For abnormal change from baseline, this is the number of patients with both baseline and post baseline evaluations.
n is the number of patients meeting the criteria at least once.
Baseline is defined as the average of all pre-dose ECG values (scheduled/unscheduled) on Day 1.
At other time points, where multiple measurements are taken the average value is used.
Change from baseline: post baseline – baseline.
Unscheduled visits are included.

Table 13 Number (%) of patients with notable ECGs for patients at RDE with extensive ECG evaluation schedule (Safety analysis set)

	Ribociclib		
	600 mg N=68 All Total n (%)	600 mg liquid N=8 All Total n (%)	Pooled 600 mg[1] N=76 All Total n (%)
QTcF (msec)			
New ≥ 450	48 (22, 45.8)	8 (4, 50.0)	56 (26, 46.4)
New >480	48 (3. 6.3)	8 (1, 12.5)	56 (4, 7.1)
New >500	48 (1, 2.1)	8 (0, 0)	56 (1, 1.8)
Increase from baseline >30	48 (31, 64.6)	8 (7, 87.5)	56 (38, 67.9)
Increase from baseline >60	48 (5, 10.4)	8 (1, 12.5)	56 (6, 10.7)
QTcB (msec)			
New ≥ 450	48 (40, 83.3)	7 (6, 85.7)	55 (46, 83.6)
New >480	48 (10, 20.8)	8 (4, 50.0)	56 (14, 25.0)
New >500	48 (1, 2.1)	8 (1, 12.5)	56 (2, 3.6)
Increase from baseline >30	48 (34, 70.8)	8 (7, 87.5)	56 (41, 73.2)
Increase from baseline >60	48 (5, 10.4)	8 (0, 0)	56 (5, 8.9)
QT (msec)			
New ≥ 450	48 (15, 31.3)	8 3 (37.5)	56 (18, 32.1)
New >480	48 (5, 10.4)	8 (1, 12.5)	56 (6, 10.7)
New >500	48 (3, 6.3)	8 (0, 0)	56 (3, 5.4)
Increase from baseline >30	48 (42, 87.5)	8 (7, 87.5)	56 (49, 87.5)
Increase from baseline >60	48 (13, 27.1)	8 (3, 37.5)	56 (16, 28.6)
VR (bpm)			
Mean RR decrease >25% & to a value >100	48 (6, 12.5)	8 (0, 0)	56 (6, 10.7)

	Ribociclib		
	600 mg N=68 All Total n (%)	**600 mg liquid N=8 All Total n (%)**	**Pooled 600 mg[1] N=76 All Total n (%)**
Mean RR increase >25% & to a value <50	48 (0, 0)	8 (0, 0)	56 (0, 0)
PR (msec)			
Increase from baseline >25% & to a value >200	48 (1, 2.1)	8 (0, 0)	56 (1, 1.8)
QRS (msec)			
Increase from baseline >25% & to a value >110	48 (0, 0)	8 (0, 0)	56 (0, 0)

[1] 3 weeks on/1 week off

New = Newly occurring post baseline value not present at baseline.
Total = number of subjects at risk for a specific category. New abnormality post-baseline = the number of subjects with at least one post-baseline and clock-time matched baseline, with baseline not meeting the criteria.
Abnormal change from baseline = number of subjects with at least one post-baseline and clock-time matched baseline.
n is the number of subjects meeting the criteria at least once.
Baseline on Day -1 for 0, 1, 2, 4, 6, 8 hours is defined as the average of pre-dose ECG values at each timepoint
Change from baseline: post baseline – clock-time matched baseline
At other time points, where multiple measurements are taken the average value is used.
Unscheduled visits are not included

Table 14 Summary of single dose and steady state ribociclib PK parameters for oral 600 mg solution formulation of ribociclib

Treatment	Statistics	Tmax C1D1 (h)	Cmax C1D1 (ng/mL)	AUC0-24h C1D1 (h*ng/mL)	Cmax C1D18/21 (ng/mL)	AUC0-24h C1D18/21 (h*ng/mL)	T 1/2, acc C1D18/21 (h)	CL/F C1D18/21 (mL/h)	Racc (AUC) C1D18/21
Ribociclib 600 mg liquid (n=8)	n	8	8	7	6	5	5	5	5
	Mean (SD)		1270 (752)	10000 (7560)	2850 (1590)	27400 (15900)	75.3 (73.0)	27100 (12200)	5.05 (4.37)
	CV% mean		59.3	75.3	55.6	58.1	96.9	44.9	86.5
	Geo-mean		1030	7720	2530	24400	57.6	24600	4.09
	CV% geo-mean		86.4	97.2	56.3	55.9	85.5	56.5	74.1
	Median	1.13	1230	8960	2080	24500	48.0	24500	3.41
	[Min; Max]	[1.08; 2.12]	[294; 2350]	[2160; 24000]	[1400; 5210]	[15000; 54100]	[29.4; 205]	[11000; 40100]	[2.31; 12.8]
Ribociclib 600 mg pooled (n=74)	n	73	73	68	57	54	49	53	50
	Mean (SD)		1170 (699)	11300 (6560)	2130 (1260)	28400 (18100)	37.3 (20.8)	30200 (18300)	2.75 (1.24)
	CV% mean		59.8	58.1	58.9	63.7	55.7	60.6	44.9
	Geo-mean		992	9700	1820	23800	32.0	25500	2.51
	CV% geo-mean		64.4	62.0	62.4	66.0	63.2	65.7	45.6
	Median	2.08	1010	10500	1690	23700	34.5	25300	2.60
	[Min; Max]	[0.917; 7.95]	[176; 3270]	[1590; 35400]	[606; 6170]	[6770; 90600]	[8.06; 97.9]	[6630; 88600]	[0.972; 6.40]

Table 15 Number of positive cells for p-pRb IHC biomarkers from tumor biopsy

	Ribociclib				
End point values	**600 mg**	**600mg liquid**	**900 mg**	**70 mg**	**600 mg - continuous regimen**
Number of subjects analysed	7	1	1	1	2
Units: H-score median (inter-quartile range (Q1-Q3))					
Baseline	90.0 (60.0 to 165.0)	200.0 (200.0 to 200.0)	110.0 (110.0 to 110.0)	120.0 (120.0 to 120.0)	185.0 (140.0 to 230.0
Steady state	100.0 (60.0 to 160.0)	200.0 (200.0 to 200.0)	85.0 (85.0 to 85.0)	60.0 (60.0 to60.0)	122.5 (115.0 to 130.0)

Table 16 Number of positive cells for KI67 from tumor biopsy

	Ribociclib				
End point values	**600 mg**	**600mg liquid**	**900 mg**	**70 mg**	**600 mg continuous regimen**
Number of subjects analysed	11	2	1	1	2
Units: Ki67 H-score median (inter-quartile range (Q1-Q3))					
Baseline	30.0 (20.0 to 50.0)	92.5 (90.0 to 95.0)	45.0 (45.0 to 45.0)	30.0 (30.0 to 30.0)	47.5 (45.0 to 50.0)
Steady State	7.0 (1.0 to 20.0)	72.5 (65.0 to 80.0)	20.0 (20.0 to 20.0)	35.0 (35.0 to 35.0)	15.5 (1.0 to 30.0)

Summary of Safety

Safety Results

All-Cause Mortality

	LEE011@50 mg N = 4	LEE011@70 mg N = 2	LEE011@140 mg N = 4	LEE011@260 mg N = 4	LEE011@280 mg N = 4	LEE011@350 mg N = 5	LEE011@400 mg N = 5	LEE011@600 mg N = 68	LEE011@600 mg@liquid@form. N = 8	LEE011@Pooled@600 mg N = 76	LEE011@750 mg N = 14	LEE011@900 mg N = 13	LEE011@1200 mg N = 3	All@subjects@3wk on/@1 wk off N = 134	LEE011@300 mg@28d@cont. N = 6	LEE011@400 mg@28d@cont. N = 6	LEE011@600 mg@28d@cont. N = 7	All@subjects@28d@cont. N = 19
Total participants affected	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	7 (10.29%)	1 (12.50%)	8 (10.53%)	2 (14.29%)	2 (15.38%)	2 (66.67%)	18 (13.43%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 7 month/years
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment

	LEE011@50 mg N = 4	LEE011@70 mg N = 2	LEE011@140 mg N = 4	LEE011@260 mg N = 4	LEE011@280 mg N = 4	LEE011@350 mg N = 5	LEE011@400 mg N = 5	LEE011@600 mg N = 68	LEE011@600 mg@liquid@form. N = 8	LEE011@Pooled@600 mg N = 76	LEE011@750 mg N = 14	LEE011@900 mg N = 13	LEE011@1200 mg N = 3	All@subjects@3wk on/@1 wk off N = 134	LEE011@300 mg@28d@cont. N = 6	LEE011@400 mg@28d@cont. N = 6	LEE011@600 mg@28d@cont. N = 7	All@subjects@28d@cont. N = 19
Total participants affected	3 (75.00%)	0 (0.00%)	1 (25.00%)	1 (25.00%)	1 (25.00%)	1 (20.00%)	1 (20.00%)	26 (38.24%)	3 (37.50%)	29 (38.16%)	5 (35.71%)	4 (30.77%)	3 (100.00%)	49 (36.57%)	0 (0.00%)	2 (33.33%)	3 (42.86%)	5 (26.32%)

Blood And Lymphatic System Disorders																		
Anaemia	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%)	1 (33.33%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Febrile Neutropenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Neutropenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (5.26%)
Thrombocytopenia	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%)	1 (7.14%)	0 (0.00%)	1 (33.33%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac Disorders																		
Pericardial 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%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal Disorders																		
Abdominal Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anal Haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Diarrhoea	0 (0.00%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Dysphagia	0 (0.00%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	2 (1.49%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Intestinal Perforation	0 (0.00%)	0 (0.0%)	1 (25.00%)	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 (0.0%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Nausea	0 (0.00%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.41%)	0 (0.00%)	3 (3.95%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	3 (2.24%)	0 (0.0%)	0 (0.0%)	1 (14.29%)	1 (5.26%)
Pancreatitis	0 (0.00%)	0 (0.0%)	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 (0.0%)	0 (0.00%)	0 (0.0%)	1 (16.67%)	0 (0.0%)	1 (5.26%)
Pneumoperitoneum	0 (0.00%)	0 (0.0%)	1 (25.00%)	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 (0.0%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Stomatitis	1 (25.00%)	0 (0.0%)	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 (0.0%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Vomiting	0 (0.00%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.41%)	0 (0.00%)	3 (3.95%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	3 (2.24%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
General Disorders And Administration Site Conditions																		
Asthenia	0 (0.00%)	0 (0.0%)	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%)	1 (33.33%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
General Physical	0 (0.00%)	0 (0.0%)	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%)	1 (33.33%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)

Health Deterioration																		
Generalised Oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Multiple Organ Dysfunction Syndrome	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	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%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatobiliary Disorders																		
Bile Duct Obstruction	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cholestasis	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Jaundice	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections And																		

Infestations																		
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Corneal Abscess	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Device Related Infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Escherichia Bacteraemia	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes Simplex	1 (25.00%)	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%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Influenza	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (5.26%)
Pneumonia	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Septic 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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sialoadenitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper Respi	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

ratory Tract Infection																		
Urinary Tract Infection	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00 %)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Injury, Poisoning And Procedural Complications																		
Overdose	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00 %)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Investigations																		
Blood Bilirubin Increased	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00 %)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	2 (1.49 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Blood Creatinine Increased	0 (0.00%)	0 (0.0 0%)	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 (7.14%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Electrocardiogram Qt Prolonged	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Transaminases Increased	0 (0.00%)	0 (0.0 0%)	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 (7.14%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)

Metabolism And Nutrition Disorders																		
Decreased Appetite	0 (0.00%)	0 (0.0 0%)	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%)	1 (33.33%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Dehydration	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00 %)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Failure To Thrive	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00 %)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Musculoskeletal And Connective Tissue Disorders																		
Back Pain	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00 %)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Bone Pain	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00 %)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Flank Pain	0 (0.00%)	0 (0.0 0%)	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 (7.14%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Musculoskeletal Pain	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00 %)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)

Neck Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain In Extremity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)																		
Malignant Ascites	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rectal Adenocarcinoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Transitional Cell Carcinoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous System Disorders																		
Akathisia	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%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Cerebrovascular Accident	0 (0.00%)	0 (0.0 0%)	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 (7.69%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Ischaemic Stroke	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00 %)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Lethargy	0 (0.00%)	0 (0.0 0%)	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 (7.14%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Migraine	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00 %)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Spinal Cord Compression	0 (0.00%)	0 (0.0 0%)	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%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Psychiatric Disorders																		
Confusional State	0 (0.00%)	0 (0.0 0%)	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 (7.14%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Delirium	0 (0.00%)	0 (0.0 0%)	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 (7.14%)	0 (0.00%)	0 (0.0 0%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Respiratory, Thoracic And Mediastinal Disorders																		

Cough	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%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	4 (5.88%)	1 (12.50%)	5 (6.58%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	7 (5.22%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Hypoxia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lung Disorder	1 (25.00%)	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%)	0 (0.00%)	1 (0.75%)	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Pneumothorax	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary Embolism	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular Disorders																		
Superior Vena Cava Syndrome	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 7 month/years

Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LEE011@50 mg N = 4	LEE011@70 mg N = 2	LEE011@140 mg N = 4	LEE011@260 mg N = 4	LEE011@280 mg N = 4	LEE011@350 mg N = 5	LEE011@400 mg N = 5	LEE011@600 mg N = 68	LEE011@600 mg@liquid@form. N = 8	LEE011@Pooled@600 mg N = 76	LEE011@750 mg N = 14	LEE011@900 mg N = 13	LEE011@1200 mg N = 3	All@subjects@3wk on/@1wk off N = 134	LEE011@300 mg@28d@cont. N = 6	LEE011@400 mg@28d@cont. N = 6	LEE011@600 mg@28d@cont. N = 7	All@subjects@28d@cont. N = 19
Total participants affected	4 (100.00%)	2 (100.00%)	4 (100.00%)	4 (100.00%)	4 (100.00%)	5 (100.00%)	5 (100.00%)	68 (100.00%)	8 (100.00%)	76 (100.00%)	14 (100.00%)	13 (100.00%)	3 (100.00%)	134 (100.00%)	5 (83.33%)	6 (100.00%)	7 (100.00%)	18 (94.74%)
Blood And Lymphatic System Disorders																		
Anaemia	2 (50.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	4 (80.00%)	2 (40.00%)	22 (32.35%)	0 (0.00%)	22 (28.95%)	5 (35.71%)	6 (46.15%)	3 (100.00%)	45 (33.58%)	2 (33.33%)	1 (16.67%)	2 (28.57%)	5 (26.32%)
Anaemia Megaloblastic	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Leukopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (25.00%)	2 (40.00%)	2 (40.00%)	15 (22.06%)	0 (0.00%)	15 (19.74%)	1 (7.14%)	7 (53.85%)	0 (0.00%)	29 (21.64%)	0 (0.00%)	0 (0.00%)	2 (28.57%)	2 (10.53%)

Lymphopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (50.00%)	1 (25.00%)	1 (20.00%)	0 (0.00%)	9 (13.24%)	0 (0.00%)	9 (11.84%)	0 (0.00%)	5 (38.46%)	1 (33.33%)	19 (14.18%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	2 (10.53%)
Neutropenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (40.00%)	2 (40.00%)	21 (30.88%)	4 (50.00%)	25 (32.89%)	6 (42.86%)	8 (61.54%)	2 (66.67%)	46 (34.33%)	3 (50.00%)	2 (33.33%)	3 (42.86%)	8 (42.11%)
Thrombocytopenia	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (40.00%)	1 (20.00%)	16 (23.53%)	1 (12.50%)	17 (22.37%)	4 (28.57%)	4 (30.77%)	2 (66.67%)	32 (23.88%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	2 (10.53%)
Cardiac Disorders																		
Arrhythmia	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Atrioventricular Block First Degree	0 (0.00%)	0 (0.00%)	1 (25.00%)	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%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sinus Tachycardia	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	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 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Ear And Labyrinth Disorders																		

Ear Discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ear Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypoacusis	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tinnitus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (1.47%)	1 (12.50%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Endocrine Disorders																		
Hypothyroidism	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye Disorders																		
Diplopia	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dry Eye	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (5.26%)
Eye Disorder	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye 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%)	1 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (5.26%)

Eye Swelling	0 (0.00 %)	1 (50.00 %)	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%)	1 (0.75 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lacrimation Increased	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	1 (12.50%)	3 (3.95 %)	0 (0.00%)	1 (7.69%)	0 (0.00%)	4 (2.99 %)	0 (0.00%)	1 (16.67%)	1 (14.29%)
Vision Blurred	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	2 (2.94%)	0 (0.00%)	2 (2.63 %)	1 (7.14%)	0 (0.00%)	0 (0.00%)	4 (2.99 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal Disorders																	
Abdominal Discomfort	0 (0.00 %)	0 (0.00 %)	1 (25.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.32 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal Distension	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (25.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.32 %)	1 (7.14%)	0 (0.00%)	0 (0.00%)	3 (2.24 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal Pain	0 (0.00 %)	1 (50.00 %)	1 (25.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	14 (20.59%)	0 (0.00%)	14 (18.42%)	0 (0.00%)	2 (15.38 %)	1 (33.33%)	19 (14.18%)	2 (33.33%)	1 (16.67%)	3 (42.86%)	6 (31.58 %)
Abdominal Pain Lower	0 (0.00 %)	1 (50.00 %)	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 (7.14%)	0 (0.00%)	0 (0.00%)	2 (1.49 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal Pain Upper	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (25.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (10.29 %)	0 (0.00%)	7 (9.21 %)	0 (0.00%)	1 (7.69%)	0 (0.00%)	9 (6.72 %)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)

Ascites	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (25.00%)	1 (20.00%)	0 (0.00%)	1 (1.47%)	1 (12.50%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (3.73%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Chapped Lips	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Constipation	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (50.00%)	1 (20.00%)	1 (20.00%)	14 (20.59%)	3 (37.50%)	17 (22.37%)	4 (28.57%)	2 (15.38%)	1 (33.33%)	30 (22.39%)	1 (16.67%)	2 (33.33%)	1 (14.29%)	4 (21.05%)
Diarrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (40.00%)	1 (20.00%)	24 (35.29%)	5 (62.50%)	29 (38.16%)	6 (42.86%)	8 (61.54%)	2 (66.67%)	49 (36.57%)	1 (16.67%)	4 (66.67%)	1 (14.29%)	6 (31.58%)
Dry Mouth	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	2 (1.49%)	0 (0.0 0%)	1 (16.67%)	0 (0.0 0%)	1 (5.26%)
Dyspepsia	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	5 (7.35%)	0 (0.0 0%)	5 (6.58%)	1 (7.14%)	1 (7.69%)	0 (0.00%)	9 (6.72%)	0 (0.0 0%)	1 (16.67%)	0 (0.0 0%)	1 (5.26%)
Dysphagia	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (7.35%)	0 (0.0 0%)	5 (6.58%)	2 (14.29%)	1 (7.69%)	1 (33.33%)	10 (7.46%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	1 (5.26%)
Flatulence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.0 0%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	1 (5.26%)
Gastrointestinal Inflammation	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 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	1 (5.26%)
Gastrointestinal Pain	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 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)

Gastrooesophageal Reflux Disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	5 (7.35%)	0 (0.00%)	5 (6.58%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	7 (5.22%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Haemorrhoids	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	2 (10.53%)
Impaired Gastric Emptying	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mouth Haemorrhage	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	0 (0.00%)	1 (50.00%)	1 (25.00%)	0 (0.00%)	2 (50.00%)	2 (40.00%)	3 (60.00%)	37 (54.41%)	5 (62.50%)	42 (55.26%)	9 (64.29%)	7 (53.85%)	3 (100.00%)	70 (52.24%)	5 (83.33%)	4 (66.67%)	3 (42.86%)	12 (63.16%)
Proctalgia	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Salivary Hypersecretion	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Stomatitis	1 (25.00%)	1 (50.00%)	0 (0.00%)	1 (25.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (21.43%)	1 (7.69%)	1 (33.33%)	9 (6.72%)	0 (0.0 0%)	1 (16.67%)	2 (28.57%)	3 (15.79%)
Toothache	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Vomiting	1 (25.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (40.00%)	2 (40.00%)	26 (38.24%)	2 (25.00%)	28 (36.84%)	6 (42.86%)	3 (23.08%)	3 (100.00%)	47 (35.07%)	0 (0.0 0%)	1 (16.67%)	3 (42.86%)	4 (21.05%)
General Disorders And Administration Site Conditions																		
Asthenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (75.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	10 (14.71%)	1 (12.50%)	11 (14.47%)	3 (21.43%)	5 (38.46%)	2 (66.67%)	26 (19.40%)	2 (33.33%)	0 (0.0 0%)	2 (28.57%)	4 (21.05%)
Chest Discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Chills	0 (0.00%)	1 (50.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	1 (5.26%)
Facial Pain	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Fatigue	2 (50.00%)	2 (100.00%)	4 (100.00%)	1 (25.00%)	1 (25.00%)	1 (20.00%)	2 (40.00%)	27 (39.71%)	4 (50.00%)	31 (40.79%)	5 (35.71%)	7 (53.85%)	1 (33.33%)	57 (42.54%)	1 (16.67%)	3 (50.00%)	4 (57.14%)	8 (42.11%)
Feeling Cold	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)

Influenza Like Illness	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	2 (10.53%)
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%)	6 (8.82%)	0 (0.00%)	6 (7.89%)	2 (14.29%)	0 (0.00%)	0 (0.00%)	8 (5.97%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	2 (10.53%)
Oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	1 (7.69%)	1 (33.33%)	5 (3.73%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oedema Peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	11 (16.18%)	0 (0.00%)	11 (14.47%)	2 (14.29%)	2 (15.38%)	2 (66.67%)	18 (13.43%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	2 (10.53%)
Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Peripheral Swelling	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyrexia	1 (25.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	11 (16.18%)	1 (12.50%)	12 (15.79%)	1 (7.14%)	1 (7.69%)	2 (66.67%)	20 (14.93%)	0 (0.00%)	1 (16.67%)	2 (28.57%)	3 (15.79%)
Hepatobiliary Disorders																		

Bile Duct Obstruction	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatocellular Injury	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperbilirubinaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune System Disorders																		
Hypersensitivity	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections And Infestations																		
Abdominal Abscess	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%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Candida 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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Conjunctivitis	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 (0.0 0%)	0 (0.00 %)	0 (0.00%)	1 (7.69%)	0 (0.00%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	1 (5.26%)
Device Related 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 (0.0 0%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	1 (5.26%)
Fungal Skin 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 (0.0 0%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.0 0%)	1 (16.67%)	0 (0.0 0%)	1 (5.26%)
Gastroenteritis	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.0 0%)	2 (2.63 %)	1 (7.14%)	0 (0.00%)	0 (0.00%)	3 (2.24 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Infection	1 (25.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Kidney 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 (0.0 0%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Lip Infection	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 (0.0 0%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Nasopharyngitis	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.0 0%)	2 (2.63 %)	1 (7.14%)	1 (7.69%)	0 (0.00%)	4 (2.99 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Oral Candidiasis	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 (0.0 0%)	0 (0.00 %)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Oral Herpes	0 (0.00 %)	0 (0.00 %)	1 (25.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.0 0%)	1 (1.32 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)

Oral 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%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Otitis Externa	0 (0.00 %)	0 (0.00 %)	1 (25.00 %)	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%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Pyuria	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Respiratory Tract 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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Sepsis	1 (25.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Sinusitis	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00 %)	1 (20.00 %)	2 (2.94%)	0 (0.0 0%)	2 (2.63%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	5 (3.73%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Staphylococcal 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 (0.0 0%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Tinea Pedis	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 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Upper Respiratory Tract Infection	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (25.00 %)	0 (0.00%)	1 (20.00 %)	8 (11.76 %)	1 (12.50%)	9 (11.84%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	11 (8.21%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)

Wound Infection	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, Poisoning And Procedural Complications																		
Contusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	1 (12.50%)	3 (3.95%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fall	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	2 (25.00%)	4 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	2 (10.53%)
Head Injury	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Limb Injury	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Radius Fracture	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations																		
Activated Partial Thromboplastin Time	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	3 (4.41%)	0 (0.00%)	3 (3.95%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (4.48%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Prolonged																	
Alanine Aminotransferase 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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Alanine Aminotransferase Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	10 (14.71%)	2 (25.00%)	12 (15.79%)	2 (14.29%)	1 (7.69%)	0 (0.00%)	17 (12.69%)	2 (33.33%)	1 (16.67%)	1 (14.29%)	4 (21.05%)
Aspartate Aminotransferase 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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aspartate Aminotransferase Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	14 (20.59%)	2 (25.00%)	16 (21.05%)	1 (7.14%)	1 (7.69%)	1 (33.33%)	21 (15.67%)	2 (33.33%)	1 (16.67%)	1 (14.29%)	4 (21.05%)
Blood Alkaline Phosphatase Increased	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	11 (16.18%)	2 (25.00%)	13 (17.11%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	16 (11.94%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)

Blood Bilirubin Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	5 (7.35%)	1 (12.50%)	6 (7.89%)	0 (0.00%)	3 (23.08%)	0 (0.00%)	11 (8.21%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
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%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood Cholesterol Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.88%)	0 (0.00%)	4 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood Creatinine Increased	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	4 (80.00%)	1 (20.00%)	10 (14.71%)	1 (12.50%)	11 (14.47%)	1 (7.14%)	3 (23.08%)	0 (0.00%)	21 (15.67%)	2 (33.33%)	2 (33.33%)	1 (14.29%)	5 (26.32%)
Blood Glucose Increased	0 (0.00%)	0 (0.00%)	1 (25.00%)	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%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood Phosphorus Decreased	0 (0.00%)	0 (0.00%)	1 (25.00%)	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%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood Thyroid Stimulating Hormone	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Increased																	
Ejection Fraction Decreased	1 (25.00%)	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%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Electrocardiogram Qt Prolonged	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	11 (16.18%)	0 (0.00%)	11 (14.47%)	3 (21.43%)	4 (30.77%)	2 (66.67%)	20 (14.93%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)
Gamma-Glutamyltransferase Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	4 (2.99%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	2 (10.53%)
Haemoglobin Decreased	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
International Normalised Ratio 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%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphocyte Count	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	14 (20.59%)	2 (25.00%)	16 (21.05%)	4 (28.57%)	1 (7.69%)	0 (0.00%)	23 (17.16%)	1 (16.67%)	0 (0.00%)	2 (28.57%)	3 (15.79%)

Decreased																	
Neutrophil Count Decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	13 (19.12%)	2 (25.00%)	15 (19.74%)	2 (14.29%)	1 (7.69%)	0 (0.00%)	18 (13.43%)	0 (0.00%)	0 (0.00%)	3 (42.86%)	3 (15.79%)
Platelet Count Decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (11.76%)	1 (12.50%)	9 (11.84%)	1 (7.14%)	2 (15.38%)	0 (0.00%)	12 (8.96%)	0 (0.00%)	0 (0.00%)	2 (28.57%)	2 (10.53%)
Thyroxine 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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Weight Decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (7.35%)	1 (12.50%)	6 (7.89%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	7 (5.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Weight Increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
White Blood Cell Count Decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	23 (33.82%)	2 (25.00%)	25 (32.89%)	4 (28.57%)	3 (23.08%)	0 (0.00%)	32 (23.88%)	3 (50.00%)	0 (0.00%)	3 (42.86%)	6 (31.58%)
Metabolism And Nutrition Disorders																		

Decreased Appetite	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (50.00%)	3 (60.00%)	1 (20.00%)	13 (19.12%)	1 (12.50%)	14 (18.42%)	3 (21.43%)	5 (38.46%)	2 (66.67%)	31 (23.13%)	2 (33.33%)	0 (0.00%)	2 (28.57%)	4 (21.05%)
Dehydration	1 (25.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.88%)	2 (25.00%)	6 (7.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (5.97%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (5.26%)
Hypercholesterolaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	4 (5.88%)	0 (0.00%)	4 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (3.73%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperglycaemia	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	1 (20.00%)	11 (16.18%)	0 (0.00%)	11 (14.47%)	3 (21.43%)	5 (38.46%)	0 (0.00%)	23 (17.16%)	0 (0.00%)	1 (16.67%)	4 (57.14%)	5 (26.32%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	3 (4.41%)	0 (0.00%)	3 (3.95%)	2 (14.29%)	0 (0.00%)	0 (0.00%)	6 (4.48%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Hypernatraemia	0 (0.00%)	1 (50.00%)	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%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypertriglyceridaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	7 (10.29%)	0 (0.00%)	7 (9.21%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	10 (7.46%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperuricaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypoalbuminaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	13 (19.12%)	0 (0.00%)	13 (17.11%)	3 (21.43%)	4 (30.77%)	0 (0.00%)	23 (17.16%)	1 (16.67%)	0 (0.00%)	1 (14.29%)	2 (10.53%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	10 (14.71%)	1 (12.50%)	11 (14.47%)	2 (14.29%)	0 (0.00%)	0 (0.00%)	15 (11.19%)	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%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	6 (8.82%)	0 (0.0 0%)	6 (7.89%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	9 (6.72%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	1 (5.26%)
Hypomagnesaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	7 (10.29%)	0 (0.0 0%)	7 (9.21%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	10 (7.46%)	1 (16.67%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.26%)
Hyponatraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	9 (13.24%)	0 (0.0 0%)	9 (11.84%)	1 (7.14%)	1 (7.69%)	0 (0.00%)	13 (9.70%)	0 (0.0 0%)	0 (0.0 0%)	2 (28.57%)	2 (10.53%)
Hypophosphataemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (10.29%)	1 (12.50%)	8 (10.53%)	2 (14.29%)	0 (0.00%)	0 (0.00%)	11 (8.21%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	1 (5.26%)
Musculoskeletal And Connective Tissue Disorders																		
Arthralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.88%)	2 (25.00%)	6 (7.89%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	7 (5.22%)	1 (16.67%)	0 (0.0 0%)	1 (14.29%)	2 (10.53%)
Back Pain	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (50.00%)	1 (20.00%)	1 (20.00%)	10 (14.71%)	1 (12.50%)	11 (14.47%)	2 (14.29%)	2 (15.38%)	0 (0.00%)	21 (15.67%)	0 (0.0 0%)	0 (0.0 0%)	2 (28.57%)	2 (10.53%)
Coccydynia	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)

Flank Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	1 (12.50%)	3 (3.95%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Groin 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%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle Atrophy	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%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle Spasms	1 (25.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	5 (7.35%)	0 (0.00%)	5 (6.58%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (5.97%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscular Weakness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	2 (10.53%)
Musculoskeletal Chest Pain	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	4 (5.88%)	1 (12.50%)	5 (6.58%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	7 (5.22%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)
Musculoskeletal Stiffness	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%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myalgia	0 (0.00%)	1 (50.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	4 (5.88%)	1 (12.50%)	5 (6.58%)	2 (14.29%)	1 (7.69%)	0 (0.00%)	12 (8.96%)	1 (16.67%)	1 (16.67%)	1 (14.29%)	3 (15.79%)

Neck Pain	0 (0.00 %)	0 (0.00 %)	1 (25.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.88%)	1 (12.50%)	5 (6.58 %)	0 (0.00%)	1 (7.69%)	0 (0.00%)	7 (5.22 %)	2 (33.33%)	0 (0.00%)	0 (0.00%)	2 (10.53 %)
Osteoarthritis	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%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain In Extremity	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	2 (50.00 %)	1 (25.00 %)	0 (0.00%)	0 (0.00%)	7 (10.29 %)	3 (37.50%)	10 (13.16%)	1 (7.14%)	2 (15.38 %)	0 (0.00%)	16 (11.94%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain In Jaw	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 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)																		
Lymphangioma	1 (25.00 %)	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%)	0 (0.00%)	1 (0.75 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tumour 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%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (33.33%)	1 (0.75 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous System Disorders																		

Allodynia	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%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Ataxia	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Balance Disorder	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Cognitive Disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2 0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Dizziness	1 (2 5.00%)	0 (0.00%)	1 (2 5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6 0.00%)	10 (14.71%)	0 (0.0 0%)	10 (13. 16%)	3 (2 1.43%)	1 (7.69%)	0 (0.00%)	19 (14. 18%)	0 (0.0 0%)	2 (33. 33%)	0 (0.0 0%)	2 (10.53%)
Dysgeusia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (7.35%)	0 (0.0 0%)	5 (6.58%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	6 (4.48%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Extrapyramidal Disorder	0 (0.00%)	0 (0.00%)	1 (2 5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.0 0%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2 0.00%)	2 (4 0.00%)	13 (19.12%)	2 (25. 00%)	15 (19. 74%)	3 (2 1.43%)	3 (2 3.08%)	0 (0.00%)	24 (17. 91%)	2 (33. 33%)	0 (0.0 0%)	1 (14. 29%)	3 (15.79%)
Hypersomnia	0 (0.00%)	0 (0.00%)	1 (2 5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Hypoaesthesia	1 (2 5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	1 (14. 29%)	1 (5.26%)

Neuralgia	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Neuropathy Peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Paraesthesia	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.88%)	0 (0.00%)	4 (5.26%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	6 (4.48%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peripheral Sensory Neuropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (1.47%)	1 (12.50%)	2 (2.63%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Somnolence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	3 (2.24%)	0 (0.00%)	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%)	1 (20.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tremor	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Visual Perseveration	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%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Product Issues																		
Device Occlusion	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)

Psychiatric Disorders																	
Anxiety	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (8.82%)	0 (0.00%)	6 (7.89%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	8 (5.97%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Confusional State	0 (0.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depression	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Hallucination	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Insomnia	1 (25.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (25.00%)	1 (20.00%)	0 (0.00%)	6 (8.82%)	0 (0.00%)	6 (7.89%)	0 (0.00%)	1 (7.69%)	1 (33.33%)	12 (8.96%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)
Irritability	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
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%)	0 (0.00%)	1 (1.47%)	1 (12.50%)	2 (2.63%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dysuria	0 (0.00%)	1 (50.00%)	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%)	1 (7.69%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Micturition Urgency	1 (25.00%)	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%)	2 (14.29%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Nephrolithiasis	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Pollakiuria	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (2.99%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Proteinuria	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	2 (1.49%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Urinary Incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	1 (12.50%)	3 (3.95%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	4 (2.99%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)
Reproductive System And Breast Disorders																		
Breast Pain	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.0%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	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%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.0%)	0 (0.0%)	1 (5.26%)
Vulvovaginal	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)

Dryness																	
Respiratory, Thoracic And Mediastinal Disorders																	
Bronchospasm	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cough	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (40.00%)	14 (20.59%)	3 (37.50%)	17 (22.37%)	1 (7.14%)	1 (7.69%)	0 (0.00%)	24 (17.91%)	1 (16.67%)	2 (33.33%)	1 (14.29%)	4 (21.05%)
Dysphonia	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	4 (5.88%)	0 (0.00%)	4 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (4.48%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)
Dyspnoea	1 (25.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (40.00%)	1 (20.00%)	12 (17.65%)	2 (25.00%)	14 (18.42%)	3 (21.43%)	0 (0.00%)	1 (33.33%)	24 (17.91%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Dyspnoea Exertional	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	1 (12.50%)	3 (3.95%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epistaxis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	3 (4.41%)	0 (0.00%)	3 (3.95%)	0 (0.00%)	1 (7.69%)	2 (66.67%)	7 (5.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemoptysis	0 (0.00%)	0 (0.00%)	1 (25.00%)	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%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Hiccups	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)

Hypoxia	1 (2 5.00 %)	0 (0 .00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	1 (1. 47%)	1 (12. 50%)	2 (2.63 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	3 (2.24 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Nasal Congestion	0 (0 .00 %)	0 (0 .00 %)	0 (0. 00%)	0 (0. 00%)	1 (2 5.00 %)	0 (0. 00%)	0 (0. 00%)	7 (1 0.29 %)	1 (12. 50%)	8 (10.5 3%)	1 (7. 14%)	0 (0. 00%)	0 (0. 00%)	10 (7.4 6%)	0 (0.0 0%)	1 (16. 67%)	1 (14. 29%)	2 (10.53 %)
Oropharyngeal Pain	1 (2 5.00 %)	0 (0 .00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	1 (2 0.00 %)	8 (1 1.76 %)	1 (12. 50%)	9 (11.8 4%)	1 (7. 14%)	1 (7. 69%)	0 (0. 00%)	13 (9.7 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Paranasal Sinus Hypersecretion	0 (0 .00 %)	0 (0 .00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	1 (1. 47%)	0 (0.0 0%)	1 (1.32 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	1 (14. 29%)	1 (5.26%)
Pleural Effusion	0 (0 .00 %)	0 (0 .00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	2 (2. 94%)	1 (12. 50%)	3 (3.95 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	3 (2.24 %)	0 (0.0 0%)	0 (0.0 0%)	1 (14. 29%)	1 (5.26%)
Pneumonitis	0 (0 .00 %)	0 (0 .00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	1 (1. 47%)	0 (0.0 0%)	1 (1.32 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	1 (0.75 %)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	1 (5.26%)
Productive Cough	1 (2 5.00 %)	0 (0 .00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	2 (2. 94%)	2 (25. 00%)	4 (5.26 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	5 (3.73 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Pulmonary Embolism	0 (0 .00 %)	0 (0 .00 %)	0 (0. 00%)	0 (0. 00%)	1 (2 5.00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Respiratory Failure	1 (2 5.00 %)	0 (0 .00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	1 (0.75 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)

Respiratory Tract Congestion	1 (25.00%)	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%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Rhinitis Allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Rhinorrhoea	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (1.47%)	1 (12.50%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (3.73%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	1 (5.26%)
Sinus Congestion	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Sneezing	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Upper-Airway Cough Syndrome	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Wheezing	1 (25.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	2 (25.00%)	4 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (4.48%)	0 (0.0 0%)	1 (16.67%)	0 (0.0 0%)	1 (5.26%)
Skin And Subcutaneous Tissue Disorders																		

Alopecia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	3 (37.50%)	5 (6.58%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	6 (4.48%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dermatitis	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%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)
Dermatitis Acneiform	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (20.00%)	2 (2.94%)	0 (0.00%)	2 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dry Skin	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (20.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	4 (2.99%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Erythema	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (14.29%)	1 (7.69%)	0 (0.00%)	7 (5.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperhidrosis	0 (0.00%)	1 (50.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	2 (2.94%)	1 (12.50%)	3 (3.95%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	7 (5.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nail Discolouration	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%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nail Disorder	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%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nail Ridging	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Night Sweats	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Onychoclasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)

Onychomadesis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Palmar-Plantar Erythrodysaesthesia Syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)
Photosensitivity Reaction	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (5.26%)
Pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	2 (4.00%)	8 (1.76%)	1 (12.50%)	9 (11.84%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	12 (8.96%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)
Rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	1 (2.00%)	5 (7.35%)	0 (0.00%)	5 (6.58%)	0 (0.00%)	1 (7.69%)	1 (33.33%)	9 (6.72%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash Erythematous	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash Generalised	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash Maculo-Papular	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	1 (12.50%)	3 (3.95%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	6 (4.48%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (5.26%)

Skin Disorder	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin Lesion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (5.26%)
Skin Mass	1 (25.00%)	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%)	1 (7.69%)	0 (0.00%)	2 (1.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular Disorders																		
Aortic Thrombosis	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Deep Vein Thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)	1 (12.50%)	3 (3.95%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (2.24%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Flushing	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)
Haematoma	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 (12.50%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hot Flush	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%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	2 (1.49%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)
Hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.88%)	0 (0.00%)	4 (5.26%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	6 (4.48%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (5.26%)

Hypotension	1 (25.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (1.32%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	4 (2.99%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Lymphoedema	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 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Phlebitis	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 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)
Thrombosis	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 (0.0 0%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	0 (0.00%)	1 (0.75%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)

Other Relevant Findings

Not applicable

Conclusion:

- The MTD and RDE for the 3 weeks on/1 week off regimen were 900 mg and 600 mg, respectively (details were provided in the interim CSR).
- No MTD or RDE was established for the once daily continuous 28-day cycle regimen. Based on review of all safety, PK data and BLRM results, it was concluded that further exploration of the continuous dosing regimens would be needed to establish MTD/RDE, however, as no additional subjects were enrolled, no further exploration was done in this study.
- Five subjects achieved a PR; four subjects treated on the once daily 3 weeks on/1 week off regimen (details were provided in the interim CSR) and one subject treated on the once daily continuous 28-day cycle.
- Increased ΔQTcF was associated with increased ribociclib exposure.
- Ribociclib was associated with a manageable safety profile that is generally consistent with previous experience with the drugs of the same class. Most of the events were transient and reversible. No new safety concerns emerged since the interim CSR.

Date of Clinical Trial Report

22-November-2017