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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Trametinib, ribociclib

Trial Indication(s)

Solid tumors

Protocol Number

CTMT212X2106

Protocol Title

A phase I/II study of safety and efficacy of ribociclib (LEE011) in combination with trametinib (TMT212) in patients with metastatic or advanced solid tumors

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase IB/II

Study Start/End Dates

Study Start Date: June 2016 (Actual)
Primary Completion Date: September 2019 (Actual)

Study Completion Date: September 2019 (Actual)

Reason for Termination (If applicable)

Upon careful review of all available efficacy and safety data from the study Phase Ib part, Novartis decided to not start the study Phase II part. This decision was in no means triggered by an unfavorable safety profile of the combination. The observed safety profile of the combination represents contributions of the individual safety profile of trametinib and ribociclib. No new safety signals were observed.

Study Design/Methodology

This study design consisted of two parts: Phase Ib and Phase II. The Phase Ib part was a multi-center, open-label, dose escalation to determine the maximum tolerated dose (MTD)/ Recommended Phase II regimen (RP2R) of trametinib and ribociclib in metastatic and advanced solid tumors independently of their RAS mutation status. Phase Ib was planned to be followed by a Phase II part to evaluate the clinical efficacy and safety of the combination of ribociclib and trametinib in subjects with advanced or metastatic pancreatic or KRAS-mutant colorectal cancer. Based on the totality of the data generated in the Phase Ib part, the Phase II part was not pursued, and the study was closed after completion of the Phase Ib part of the study.

Dose escalation/de-escalation were guided through a Bayesian Logistic Regression Model (BLRM) with escalation with overdose control (EWOC) principle. A minimum of 3 evaluable subjects were treated at the starting dose of trametinib and ribociclib for minimum of one cycle. After each cohort of subjects, the candidate dose combinations were the ones fulfilling the overdose criterion that there is less than 25% chance of excessive toxicity. Additional cohorts continued until the MTD and/or RP2R was established. Evaluable subjects were those who have had at least 75% of the planned doses for each of the assigned combination drugs and/or who experience a DLT during the first cycle.

Subjects with advanced or metastatic solid tumors independently of the RAS mutation status were screened for eligibility during the 28 days prior to starting study treatment on Cycle 1 Day 1. The eligibility assessments were performed and ensured that all inclusion and exclusion were satisfied.

The Phase Ib part started by investigating the approved dose of trametinib (2 mg daily), in combination with ribociclib 200 mg, with the option to escalate ribociclib up to 600 mg. Based on the safety data obtained from this first dosing cohort, the study design was amended to investigate two alternate dosing schedules of the combination treatment:

- Schedule 1 (trametinib administered once daily from Day 1 to Day 14, and ribociclib administered once daily from Day 8 to Day 21 of a 21-day cycle). This schedule was assessed in successive cohorts of subjects receiving trametinib 1.5 to 2 mg and increasing doses of ribociclib (150 to 600 mg).

- Schedule 2 (trametinib and ribociclib administered once daily from Day 1 to Day 14 of a 21-day cycle). Schedule 1 was assessed in successive cohorts of subjects receiving trametinib (1.5 to 2 mg) and increasing doses of ribociclib (150 to 600 mg).

Based on the review of emerging safety and pharmacokinetic data from different treatment cohorts within those two treatment schedules, additional cohorts (Cohort Xa and Xb) were investigated: Cohort Xa (trametinib 1 mg once daily in combination with ribociclib 300 mg once daily with, Schedule 1) and Cohort Xb (trametinib 1 mg once daily in combination with ribociclib 400 mg once daily with, Schedule 1) were conducted in parallel.

There was no fixed treatment duration; subjects were treated until documented disease progression, intolerable toxicity, withdrawal of consent, discontinuation at the discretion of the Investigator, or premature termination of the study.

Centers

15 centers in 7 countries: Netherlands(2), United States(6), Australia(1), Belgium(1), Canada(2), Germany(2), Spain(1)

Objectives:

Phase Ib:
The primary objective of Phase Ib part was to define the MTD and/or the RP2R of ribociclib and trametinib in patients with solid tumors.
The secondary objectives of Phase Ib part included: to evaluate the safety and tolerability of ribociclib in combination with trametinib and to assess the preliminary anti-tumor activity of ribociclib in combination with trametinib.

Phase II:
The primary objective of Phase II part was to assess overall response rate (ORR) with the combination of ribociclib and trametinib in patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and in patients with advanced or metastatic KRAS-mutant colorectal carcinoma who have failed at least two prior lines of treatment.
The secondary objectives of Phase II part included: To evaluate the safety and tolerability, duration of response (DOR), disease control rate (DCR), time to response (TTR), overall survival (OS), and progression-free survival (PFS) of ribociclib in combination with trametinib
The Phase II part was not pursued, and the study was closed after completion of the Phase Ib part of the study.

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

Ribociclib (LEE011) was supplied in the form of 50 mg capsules and 200 mg tablets for oral administration. Ribociclib was escalated from 200 to 600 mg at different dosing schedules: 1) once daily on days 1 to 21 of a 28 days cycle; 2) once daily on days 8 to 21 of a 21-day cycle (Schedule 1); and 3) once daily on days 1 to 14 of a 21-day cycle (Schedule 2).

Trametinib was supplied in the form of 0.5 mg and 2 mg tablets for oral administration. Trametinib was administered at different dose strengths (0.5, 1, 1.5 or 2 mg) and at different dosing schedules: 1) once daily on days 1 to 21 of a 28-day cycle; 2) once daily on days 1 to 14 of a 21-day cycle (Schedule 1 and Schedule 2).

Statistical Methods

The primary endpoint for the dose escalation part of the study was the DLT rate observed during Cycle 1. Frequency of DLTs at each dose level associated with administration of ribociclib and trametinib in a 21-day cycle were calculated on the dose-determining set: all patients who received at least one dose of ribociclib and trametinib in the dose escalation phase who had met the minimum safety evaluation requirements and the minimum exposure criterion or had experienced DLT during the first cycle of combination treatment.

The secondary efficacy objectives for the dose escalation part of the study were to assess the progression disease rate (PDR) and progression free survival (PFS) of the combination treatment. PDR and PFS assessments were performed based on the Full Analysis Set: all patients who received at least one dose of either study drug.

PDR was defined as the proportion of subjects with a progressive disease as their best overall response (BOR) as assessed per RECIST 1.1 by Investigator assessment. PDR was estimated and the 95% CI was provided by treatment group.

PFS was defined as the time from the date of the first dose of study treatment to the date of first documented disease progression per RECIST 1.1 or death due to any cause. PFS was described in tabular and graphical format using Kaplan-Meier methods, including estimated median (in months) with 95% CI.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria (All):
• Written informed consent must
• Patient has histologically and/or cytologically confirmed malignancies:

Phase I:
• Patients with advanced or metastatic solid tumors who have failed at least one prior line of systemic antineoplastic therapy in the advanced setting without a standard of care treatment option available;

Phase II:
• Advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic antineoplastic therapies in the advanced setting
• Advanced or metastatic KRAS-mutant CRC who have failed at least two prior systemic antineoplastic therapies in the advanced setting without a standard of care treatment option available. Testing for KRAS mutation in patients with CRC using locally approved diagnostic kit will be used for eligibility.
• Phase II only: patient must have measurable disease
• Patient has an ECOG performance status 0 or 1.
• Patient has adequate bone marrow and organ function
• Patient must have specified laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of study medication on Cycle 1 Day 1:
• Standard 12-lead ECG values defined

Exclusion Criteria:
Phase II only:
• Patient has received prior treatment with a MEK inhibitor or a CDK4/6 inhibitor.

Phase I and Phase II:

• Patient with a known hypersensitivity to the study drugs or any of the excipients of ribociclib or trametinib.
• Patient is concurrently using other anti-cancer therapy.
• Patient has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to Cycle 1 Day 1
• Patient has received local therapy to liver ≤ 3 months of C1D1
• History of liver disease as follow:
• Cirrhosis
• Autoimmune hepatitis
• Active viral hepatitis
• Portal hypertension
• Drug induced liver steatosis
• Prior systemic anti-cancer treatment within 28 days prior to Cycle 1 Day 1
• Prior therapy with anthracyclines at cumulative doses of 450 mg/ m2 or more for doxorubicin or 900 mg/m2 or more for epirubicin.
• Patient is currently receiving warfarin or other coumadin derived anti-coagulant
• Patient has a history of deep venin thrombosis or pulmonary embolism within 6 months of screening.
• Patient has a concurrent malignancy or malignancy within 3 years prior to Cycle 1 Day 1, with the exception of adequately treated basal or squamous cell carcinoma or curatively resected cervical cancer.
• Patients with central nervous system (CNS) involvement
• Patient has impairment of GI function or GI disease that may significantly alter the absorption of the study drugs
• History of interstitial lung disease or pneumonitis.
• Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality
• Patient is currently receiving any strong inducers or inhibitors of CYP3A4/5 and/or Substances that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5 and cannot be discontinued 7 days prior to Cycle 1 Day 1:
• Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
• History of retinal vein occlusion (RVO)

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Overall Study

	Phase I-TMT212+LEE011	Phase II-TMT212+LEE011	Total
Arm/Group Description	Patients with advanced or metastatic solid tumors who received combination treatment with ribociclib (projected dose levels: 0.5 mg, 1 mg, 1.5 mg and 2 mg) and trametinib (projected dose levels: 200 mg, 300 mg, 400 mg, 500 mg and 600 mg) at different dosing regimens.	Patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and patients with advanced or metastatic KRAS-mutant colorectal carcinoma who have failed at least two prior lines of treatment.	
Started	95	0[1]	95
Full analysis set	95	0	95
Safety set	95	0	95
Dose determining set	79	0	79
Completed	0	0	0
Not Completed	95	0	95
Disease progression	55	0	55
Subject/guardian decision	15	0	15

Adverse Event	14	0	14
Physician Decision	8	0	8
Death	1	0	1
Lost to Follow-up	1	0	1
Sponsor decision	1	0	1

[1] Phase II part was not conducted

Baseline Characteristics

	Phase I-TMT212+LEE011	Total
Arm/Group Description	Patients with advanced or metastatic solid tumors who received combination treatment with ribociclib (projected dose levels: 0.5 mg, 1 mg, 1.5 mg and 2 mg) and trametinib (projected dose levels: 200 mg, 300 mg, 400 mg, 500 mg and 600 mg) at different dosing regimens.	
Number of Participants [units: participants]	95	95

Age Continuous (units: Years) Mean ± Standard Deviation		
	58.0±9.89	
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)		
Female	46	46
Male	49	49
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)		
Asian	5	5
Black	2	2
Caucasian	84	84
Pacific islander	1	1
Unknown	3	3

Summary of Efficacy

Primary Outcome Result(s)

Phase Ib: Number of participants with dose limiting toxicities (DLTs)

(Time Frame: 21-day cycle one of treatment)

Cohort 0: TMT212 2 mg QD + LEE011 200 mg	Cohort 1: TMT212 1.5 mg QD + LEE011 200 mg	Cohort 2a: TMT212 2 mg QD + LEE011 200 mg	Cohort 2b: TMT212 1.5 mg QD + LEE011	Cohort 3a: TMT212 2 mg QD + LEE011 300 mg	Cohort 3b: TMT212 1.5 mg QD + LEE011	Cohort 4a: TMT212 2 mg QD + LEE011 400 mg	Cohort 4a*: TMT212 2 mg QD + LEE011 400 mg	Cohort 5a: TMT212 2 mg QD + LEE011 500 mg	Cohort Xa: TMT212 1 mg QD + LEE011 300 mg	Cohort Xb: TMT212 1 mg QD + LEE011 400 mg

	21 on/7 off	QD - Schedule 1	QD- Schedule 1	300 mg QD- Schedule 1	QD- Schedule 1	400 mg QD - Schedule 1	QD - Schedule 1	QD- Schedule 2	QD- Schedule 1	QD- Schedule 1	QD- Schedule 1
Arm/Group Description	2 mg TMT212 administered once daily on Days 1-28 and 200 mg LEE011 administered once daily on Days 1-21 followed by a 7-day break of a 28-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and LEE011 administered once daily on Days 1-14 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 500 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle
Number of Participants Analyzed [units: participants]	3	6	5	5	12	10	8	9	6	9	6
Phase Ib: Incidence of dose limiting toxicities (DLTs) (units: Participants) Count of Participant											

s (Not Applicable)										
	2 (66.67%)	0 (%)	0 (%)	0 (%)	1 (8.33%)	2 (20%)	3 (37.5%)	3 (33.33%)	0 (%)	0 (%)	1 (16.67%)

Phase II: Objective Response Rate (ORR)

(Time Frame: Until progression of disease up to 1 year)

	Phase II-TMT212+LEE011
Arm/Group Description	Patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and patients with advanced or metastatic KRAS-mutant colorectal carcinoma who have failed at least two prior lines of treatment.
Number of Participants Analyzed [units: participants]	0
Phase II: Objective Response Rate (ORR) (units: Percentage of participants) Number (95% Confidence Interval)	

Secondary Outcome Result(s)

Phase Ib: Progression disease rate

(Time Frame: Until progression of disease, up to approximately 2 years)

	Cohort 0: TMT212 2 mg QD + LEE011 200 mg 21 on/7 off	Cohort 1: TMT212 1.5 mg QD + LEE011 200 mg QD - Schedule 1	Cohort 2a: TMT212 2 mg QD + LEE011 200 mg QD- Schedule 1	Cohort 2b: TMT212 1.5 mg QD + LEE011 300 mg QD- Schedule 1	Cohort 3a: TMT212 2 mg QD + LEE011 300 mg QD- Schedule 1	Cohort 3b: TMT212 1.5 mg QD + LEE011 400 mg QD - Schedule 1	Cohort 4a: TMT212 2 mg QD + LEE011 400 mg QD - Schedule 1	Cohort 4a*: TMT212 2 mg QD + LEE011 400 mg QD- Schedule 2	Cohort 5a: TMT212 2 mg QD + LEE011 500 mg QD- Schedule 1	Cohort Xa: TMT212 1 mg QD + LEE011 300 mg QD- Schedule 1	Cohort Xb: TMT212 1 mg QD + LEE011 400 mg QD- Schedule 1
Arm/Group Description	2 mg TMT212 administered once daily on Days 1-28 and 200 mg LEE011 administered once daily on Days 1-21 followed by a 7-day break of a 28-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and LEE011 administered once daily on Days 1-14 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 500 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle
Number of Participants Analyzed [units:	5	7	6	5	12	12	10	9	10	10	9

participants]											
Phase Ib: Progression disease rate (units: Percentage of Participants) Number (95% Confidence Interval)											
	20.0 (0.5 to 71.6)	42.9 (9.9 to 81.6)	50 (11.8 to 88.2)	40 (5.3 to 85.3)	41.7 (15.2 to 72.3)	41.7 (15.2 to 72.3)	20 (2.5 to 55.6)	33.3 (7.5 to 70.1)	50 (18.7 to 81.3)	80 (44.4 to 97.5)	55.6 (21.2 to 86.3)

Phase Ib: Progression free survival (PFS)

(Time Frame: Until progression of disease or death, up to approximately 2 years)

	Phase I-TMT212+LEE011
Arm/Group Description	Patients with advanced or metastatic solid tumors who received combination treatment with ribociclib (projected dose levels: 0.5 mg, 1 mg, 1.5 mg and 2 mg) and trametinib (projected dose levels: 200 mg,

	300 mg, 400 mg, 500 mg and 600 mg) at different dosing regimens.
Number of Participants Analyzed [units: participants]	95
Phase Ib: Progression free survival (PFS) (units: Months) Median (95% Confidence Interval)	
	2.6 (1.8 to 3.2)

Phase II: Duration of response (DOR)

(Time Frame: From first documented response until progression of disease or death, up to 1 year)

	Phase II-TMT212+LEE011
Arm/Group Description	Patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and patients with advanced or metastatic KRAS-mutant colorectal carcinoma who have failed at least two prior lines of treatment.

Number of Participants Analyzed [units: participants]	0
Phase II: Duration of response (DOR) (units: Months) Mean (95% Confidence Interval)	

Phase II: Time to response

(Time Frame: From start of study drug to first documented response, up to 1 year)

	Phase II-TMT212+LEE011
Arm/Group Description	Patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and patients with advanced or metastatic KRAS-mutant colorectal carcinoma who have failed at least two prior lines of treatment.
Number of Participants Analyzed [units: participants]	0
Phase II: Time to response	

(units: Months) Mean (95% Confidence Interval)	

Phase II: Disease Control Rate (DCR)

(Time Frame: Until progression of disease, up to 1 year)

	Phase II-TMT212+LEE011
Arm/Group Description	Patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and patients with advanced or metastatic KRAS-mutant colorectal carcinoma who have failed at least two prior lines of treatment.
Number of Participants Analyzed [units: participants]	0
Phase II: Disease Control Rate (DCR) (units: Percentage of Participants) Number (95% Confidence Interval)	

Phase II: Progression Free Survival (PFS)

(Time Frame: Until progression of disease or death, up to 1 year)

	Phase II-TMT212+LEE011
Arm/Group Description	Patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and patients with advanced or metastatic KRAS-mutant colorectal carcinoma who have failed at least two prior lines of treatment.
Number of Participants Analyzed [units: participants]	0
Phase II: Progression Free Survival (PFS) (units: Months) Median (95% Confidence Interval)	

Phase II: Overall Survival (OS)

(Time Frame: Up to 1 year)

	Phase II-TMT212+LEE011
Arm/Group Description	Patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment and patients with advanced or metastatic KRAS-mutant colorectal carcinoma who have failed at least two prior lines of treatment.
Number of Participants Analyzed [units: participants]	0
Phase II: Overall Survival (OS) (units: Months) Median (95% Confidence Interval)	

Summary of Safety

Safety Results

All-Cause Mortality

	Cohort 0: TMT212 2 mg QD + LEE011 200 mg 21 on/7 off N = 5	Cohort 1: TMT212 1.5 mg QD + LEE011 200 mg QD - Schedule 1 N = 7	Cohort 2a: TMT212 2 mg QD + LEE011 200 mg QD- Schedule 1 N = 6	Cohort 2b: TMT212 1.5 mg QD + LEE011 300 mg QD- Schedule 1 N = 5	Cohort 3a: TMT212 2 mg QD + LEE011 300 mg QD- Schedule 1 N = 12	Cohort 3b: TMT212 1.5 mg QD + LEE011 400 mg QD - Schedule 1 N = 12	Cohort 4a: TMT212 2 mg QD + LEE011 400 mg QD - Schedule 1 N = 10	Cohort 4a*: TMT212 2 mg QD + LEE011 400 mg QD- Schedule 2 N = 9	Cohort 5a: TMT212 2 mg QD + LEE011 500 mg QD- Schedule 1 N = 10	Cohort Xa: TMT212 1 mg QD + LEE011 300 mg QD- Schedule 1 N = 10	Cohort Xb: TMT212 1 mg QD + LEE011 400 mg QD- Schedule 1 N = 9	All Subjects N = 95
Arm/Group Description	2 mg TMT212 administered once daily on Days 1-28 and 200 mg LEE011 administered once daily on Days 1-21 followed by a 7-day break of a 28-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and LEE011 administered once daily on Days 1-14 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 500 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	All subjects who received at least one dose of either study drug in the dose-escalation phase
Total participa	1 (20.00%)	1 (14.29%)	0 (0.00%)	1 (20.00%)	1 (8.33%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	2 (22.22%)	8 (8.42%)

nts affected

Serious Adverse Events by System Organ Class

Time Frame	Adverse Event (AE) timeframe: Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 25.53 months
Additional Description	Adverse Event (AE): Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment

	Cohort 0: TMT212 2 mg QD + LEE011 200 mg 21 on/7 off N = 5	**Cohort 1: TMT212 1.5 mg QD + LEE011 200 mg QD - Schedule 1 N = 7**	**Cohort 2a: TMT212 2 mg QD + LEE011 200 mg QD- Schedule 1 N = 6**	**Cohort 2b: TMT212 1.5 mg QD + LEE011 300 mg QD- Schedule 1 N = 5**	**Cohort 3a: TMT212 2 mg QD + LEE011 300 mg QD- Schedule 1 N = 12**	**Cohort 3b: TMT212 1.5 mg QD + LEE011 400 mg QD - Schedule 1 N = 12**	**Cohort 4a: TMT212 2 mg QD + LEE011 400 mg QD - Schedule 1 N = 10**	**Cohort 4a*: TMT212 2 mg QD + LEE011 400 mg QD- Schedule 2 N = 9**	**Cohort 5a: TMT212 2 mg QD + LEE011 500 mg QD- Schedule 1 N = 10**	**Cohort Xa: TMT212 1 mg QD + LEE011 300 mg QD- Schedule 1 N = 10**	**Cohort Xb: TMT212 1 mg QD + LEE011 400 mg QD- Schedule 1 N = 9**	**All Subjects N = 95**
Arm/Group Description	2 mg TMT212 administered once daily on Days 1-28 and 200 mg LEE011 administ	1.5 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administ	2 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administ	1.5 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administ	2 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administ	1.5 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administ	2 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administ	2 mg TMT212 administered once daily on Days 1-14 and LEE011 administered	2 mg TMT212 administered once daily on Days 1-14 and 500 mg LEE011 administ	1 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administ	1 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administ	All subjects who received at least one dose of either study drug in the

	ered once daily on Days 1-21 followed by a 7-day break of a 28-day cycle	ered once daily on Days 8-21 of a 21-day cycle	ered once daily on Days 8-21 of a 21-day cycle	ered once daily on Days 8-21 of a 21-day cycle	ered once daily on Days 8-21 of a 21-day cycle	ered once daily on Days 8-21 of a 21-day cycle	ered once daily on Days 8-21 of a 21-day cycle	once daily on Days 1-14 of a 21-day cycle	ered once daily on Days 8-21 of a 21-day cycle	ered once daily on Days 8-21 of a 21-day cycle	ered once daily on Days 8-21 of a 21-day cycle	dose-escalation phase
Total participants affected	2 (40.00 %)	1 (14.29 %)	1 (16.67 %)	2 (40.00 %)	5 (41.67 %)	4 (33.33 %)	6 (60.00 %)	6 (66.67 %)	5 (50.00 %)	2 (20.00 %)	6 (66.67 %)	40 (42.11%)
Blood and lymphatic system disorders												
Anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Thrombocytopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Eye disorders												
Retinal vein occlusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Gastrointestinal disorders												
Abdominal pain	1 (20.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	3 (3.16 %)
Constipation	0 (0.00%)	0 (0.00%)	1 (16.67 %)	1 (20.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11 %)
Dysphagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Gastrointestinal	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	2 (2.11 %)

haemorrhage												
Gastrointestinal perforation	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 (11.11%)	1 (1.05%)
Intestinal obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	2 (2.11%)
Intestinal perforation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Large intestinal obstruction	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Nausea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (22.22%)	3 (3.16%)
Obstruction gastric	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Oesophagitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Pancreatitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Small intestinal obstruction	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (20.00%)	1 (8.33%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (11.11%)	6 (6.32%)
Vomiting	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 (11.11%)	1 (1.05%)
General disorders and administration site conditions												
Administration site extravasation	0 (0.00%)	1 (14.29%)	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 (1.05%)

General physical health deterioration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Malaise	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Pyrexia	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 (20.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Hepatobiliary disorders												
Bile duct obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Cholangitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Hepatotoxicity	1 (20.00%)	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 (1.05%)
Infections and infestations												
Abdominal sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Biliary 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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Clostridium difficile 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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Pneumonia	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 (11.11%)	1 (1.05%)
Rash pustular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)

Sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Urinary 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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Urinary tract infection bacterial	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Injury, poisoning and procedural complications												
Overdose	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Investigations												
Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Blood creatinine increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Ejection fraction decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.05%)
Occult blood positive	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Metabolism and nutrition disorders												

Dehydration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Hyponatraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Musculoskeletal and connective tissue disorders												
Back pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	2 (2.11%)
Groin 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%)	1 (11.11%)	1 (1.05%)
Musculoskeletal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Nervous system disorders												
Cerebral ischaemia	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 (11.11%)	1 (1.05%)
Haemorrhage intracranial	1 (20.00%)	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 (1.05%)
Presyncope	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Renal and urinary disorders												
Acute kidney injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Respiratory, thoracic and mediastinal disorders												

Dyspnoea	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 (10.00%)	0 (0.00%)	1 (1.05%)
Pharyngeal inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Pulmonary arterial hypertension	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 (1.05%)
Skin and subcutaneous tissue disorders												
Rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Event (AE) timeframe: Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 25.53 months
Additional Description	Adverse Event (AE): Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Cohort 0: TMT212 2 mg QD + LEE011 200 mg 21 on/7	**Cohort 1: TMT212 1.5 mg QD + LEE011 200 mg QD - Schedul**	**Cohort 2a: TMT212 2 mg QD + LEE011 200 mg QD- Schedul**	**Cohort 2b: TMT212 1.5 mg QD + LEE011 300 mg QD- Schedul**	**Cohort 3a: TMT212 2 mg QD + LEE011 300 mg QD- Schedul**	**Cohort 3b: TMT212 1.5 mg QD + LEE011 400 mg QD - Schedul**	**Cohort 4a: TMT212 2 mg QD + LEE011 400 mg QD - Schedul**	**Cohort 4a*: TMT212 2 mg QD + LEE011 400 mg QD- Schedul**	**Cohort 5a: TMT212 2 mg QD + LEE011 500 mg QD- Schedul**	**Cohort Xa: TMT212 1 mg QD + LEE011 300 mg QD- Schedul**	**Cohort Xb: TMT212 1 mg QD + LEE011 400 mg QD- Schedul**	**All Subjects N = 95**

	off N = 5	e 1 N = 7	e 1 N = 6	e 1 N = 5	e 1 N = 12	e 1 N = 12	e 1 N = 10	e 2 N = 9	e 1 N = 10	e 1 N = 10	e 1 N = 9	
Arm/Group Description	2 mg TMT212 administered once daily on Days 1-28 and 200 mg LEE011 administered once daily on Days 1-21 followed by a 7-day break of a 28-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 200 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1.5 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and LEE011 administered once daily on Days 1-14 of a 21-day cycle	2 mg TMT212 administered once daily on Days 1-14 and 500 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1 mg TMT212 administered once daily on Days 1-14 and 300 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	1 mg TMT212 administered once daily on Days 1-14 and 400 mg LEE011 administered once daily on Days 8-21 of a 21-day cycle	All subjects who received at least one dose of either study drug in the dose-escalation phase
Total participants affected	5 (100.00%)	7 (100.00%)	6 (100.00%)	5 (100.00%)	12 (100.00%)	12 (100.00%)	10 (100.00%)	8 (88.89%)	10 (100.00%)	10 (100.00%)	9 (100.00%)	94 (98.95%)
Blood and lymphatic system disorders												
Anaemia	3 (60.00%)	2 (28.57%)	3 (50.00%)	2 (40.00%)	8 (66.67%)	7 (58.33%)	3 (30.00%)	5 (55.56%)	3 (30.00%)	2 (20.00%)	2 (22.22%)	40 (42.11%)
Leukopenia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	1 (10.00%)	1 (10.00%)	0 (0.00%)	5 (5.26%)
Lymphopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	2 (2.11%)

Neutropenia	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	3 (25.00%)	1 (8.33%)	1 (10.00%)	2 (22.22%)	3 (30.00%)	2 (20.00%)	1 (11.11%)	14 (14.74%)
Thrombocytopenia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	2 (20.00%)	3 (33.33%)	4 (40.00%)	1 (10.00%)	2 (22.22%)	15 (15.79%)
Cardiac disorders												
Atrioventricular block first degree	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Bradycardia	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 (11.11%)	1 (1.05%)
Mitral valve thickening	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Sinus bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Ventricular arrhythmia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Ear and labyrinth disorders												
Ear congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Tinnitus	0 (0.00%)	1 (14.29%)	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 (1.05%)
Vertigo	0 (0.00%)	1 (14.29%)	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 (1.05%)
Eye disorders												
Chorioretinopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)

Dry eye	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.16%)
Eye irritation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Eye pain	1 (20.00%)	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 (1.05%)
Eye swelling	0 (0.00%)	1 (14.29%)	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 (1.05%)
Periorbital oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Retinal detachment	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Retinal disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Retinal exudates	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Subretinal fluid	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Vision blurred	0 (0.00%)	2 (28.57%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.16%)
Visual impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Vitreous floaters	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Gastrointestinal disorders												
Abdominal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.16%)
Abdominal distension	1 (20.00%)	1 (14.29%)	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 (2.11%)
Abdominal pain	1 (20.00%)	3 (42.86%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (8.33%)	1 (10.00%)	3 (33.33%)	0 (0.00%)	1 (10.00%)	2 (22.22%)	13 (13.68%)

Abdominal pain lower	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Abdominal pain upper	1 (20.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.16%)
Anal incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Aphthous ulcer	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Ascites	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Constipation	0 (0.00%)	1 (14.29%)	2 (33.33%)	2 (40.00%)	1 (8.33%)	2 (16.67%)	3 (30.00%)	2 (22.22%)	0 (0.00%)	2 (20.00%)	2 (22.22%)	17 (17.89%)
Diarrhoea	3 (60.00%)	5 (71.43%)	2 (33.33%)	3 (60.00%)	6 (50.00%)	7 (58.33%)	4 (40.00%)	5 (55.56%)	9 (90.00%)	1 (10.00%)	5 (55.56%)	50 (52.63%)
Dry mouth	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	3 (30.00%)	2 (22.22%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	10 (10.53%)
Duodenal ulcer	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Dyspepsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	4 (4.21%)
Dysphagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Flatulence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	4 (4.21%)
Haemorrhoids	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 (11.11%)	1 (1.05%)
Intra-abdominal haematoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)

Lip dry	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Lip pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Lip swelling	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Mouth ulceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Nausea	0 (0.00%)	3 (42.86%)	4 (66.67%)	3 (60.00%)	7 (58.33%)	7 (58.33%)	3 (30.00%)	3 (33.33%)	5 (50.00%)	4 (40.00%)	5 (55.56%)	44 (46.32%)
Oesophageal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Oesophagitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Oral discomfort	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Proctalgia	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Rectal haemorrhage	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Retching	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 (1.05%)
Stomatitis	0 (0.00%)	2 (28.57%)	3 (50.00%)	2 (40.00%)	8 (66.67%)	3 (25.00%)	3 (30.00%)	5 (55.56%)	6 (60.00%)	1 (10.00%)	0 (0.00%)	33 (34.74%)
Tongue discolouration	1 (20.00%)	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 (1.05%)
Tooth loss	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Toothache	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Upper gastrointestin	0 (0.00%)	1 (14.29%)	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 (1.05%)

al haemorrhage												
Vomiting	2 (40.00 %)	5 (71.43 %)	3 (50.00 %)	1 (20.00 %)	3 (25.00 %)	5 (41.67 %)	3 (30.00 %)	5 (55.56 %)	2 (20.00 %)	3 (30.00 %)	6 (66.67 %)	38 (40.00%)
General disorders and administration site conditions												
Chills	0 (0.00%)	2 (28.57 %)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	1 (10.00 %)	1 (11.11 %)	1 (10.00 %)	1 (10.00 %)	0 (0.00%)	8 (8.42 %)
Device related thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Face oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Fatigue	3 (60.00 %)	5 (71.43 %)	3 (50.00 %)	4 (80.00 %)	8 (66.67 %)	7 (58.33 %)	6 (60.00 %)	4 (44.44 %)	5 (50.00 %)	5 (50.00 %)	4 (44.44 %)	54 (56.84%)
Gait disturbance	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Influenza like illness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Malaise	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 (10.00 %)	0 (0.00%)	1 (1.05 %)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Oedema peripheral	0 (0.00%)	1 (14.29 %)	2 (33.33 %)	1 (20.00 %)	5 (41.67 %)	5 (41.67 %)	5 (50.00 %)	3 (33.33 %)	1 (10.00 %)	1 (10.00 %)	2 (22.22 %)	26 (27.37%)
Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Peripheral swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	2 (2.11 %)

Pyrexia	1 (20.00 %)	3 (42.86 %)	1 (16.67 %)	1 (20.00 %)	4 (33.33 %)	3 (25.00 %)	2 (20.00 %)	3 (33.33 %)	3 (30.00 %)	1 (10.00 %)	0 (0.00%)	22 (23.1 6%)
Secretion discharge	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 (1.05 %)
Suprapubic 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 (10.00 %)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Swelling face	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 (10.00 %)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Temperature intolerance	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Xerosis	0 (0.00%)	1 (14.29 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11 %)
Hepatobiliary disorders												
Gallbladder obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Hepatospleno megaly	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Immune system disorders												
Contrast media reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Immune system disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Seasonal allergy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Infections and infestations												
Arthritis infective	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)

Bronchitis	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Catheter site cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Erysipelas	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 (11.11%)	1 (1.05%)
Eye infection	0 (0.00%)	1 (14.29%)	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 (1.05%)
Fungal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Herpes simplex	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Localised infection	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Paronychia	0 (0.00%)	1 (14.29%)	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 (1.05%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Postoperative wound infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Pustule	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Rash pustular	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 (10.00%)	0 (0.00%)	1 (11.11%)	2 (2.11%)
Rhinitis	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Skin infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)

Staphylococcal skin infection	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Tinea cruris	0 (0.00%)	1 (14.29%)	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 (1.05%)
Tooth infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Urinary tract infection	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (8.33%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	1 (10.00%)	1 (10.00%)	1 (11.11%)	8 (8.42%)
Viral 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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Vulvovaginal mycotic infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Injury, poisoning and procedural complications												
Ankle fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Avulsion fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Thermal burn	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Wrist fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Investigations												

Activated partial thromboplastin time prolonged	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Alanine aminotransferase increased	1 (20.00%)	0 (0.00%)	2 (33.33%)	2 (40.00%)	2 (16.67%)	2 (16.67%)	2 (20.00%)	4 (44.44%)	2 (20.00%)	0 (0.00%)	2 (22.22%)	19 (20.00%)
Amylase increased	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (11.11%)	1 (10.00%)	1 (10.00%)	2 (22.22%)	7 (7.37%)
Aspartate aminotransferase increased	1 (20.00%)	1 (14.29%)	4 (66.67%)	4 (80.00%)	5 (41.67%)	4 (33.33%)	7 (70.00%)	5 (55.56%)	4 (40.00%)	1 (10.00%)	2 (22.22%)	38 (40.00%)
Bilirubin conjugated 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%)	1 (10.00%)	0 (0.00%)	1 (1.05%)
Blood alkaline phosphatase increased	0 (0.00%)	3 (42.86%)	2 (33.33%)	2 (40.00%)	2 (16.67%)	1 (8.33%)	1 (10.00%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	2 (22.22%)	15 (15.79%)
Blood bilirubin increased	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	2 (20.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	6 (6.32%)
Blood creatine increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Blood creatine phosphokinase increased	2 (40.00%)	3 (42.86%)	3 (50.00%)	1 (20.00%)	6 (50.00%)	6 (50.00%)	4 (40.00%)	4 (44.44%)	5 (50.00%)	0 (0.00%)	3 (33.33%)	37 (38.95%)
Blood creatinine decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Blood creatinine increased	0 (0.00%)	0 (0.00%)	3 (50.00%)	0 (0.00%)	2 (16.67%)	2 (16.67%)	0 (0.00%)	2 (22.22%)	1 (10.00%)	1 (10.00%)	0 (0.00%)	11 (11.58%)
Blood urea increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)

C-reactive protein increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Ejection fraction decreased	1 (20.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (10.00%)	0 (0.00%)	4 (4.21%)
Electrocardiogram QT prolonged	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Gamma-glutamyltransferase increased	1 (20.00%)	1 (14.29%)	1 (16.67%)	1 (20.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	8 (8.42%)
International normalised ratio increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Lipase increased	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	1 (10.00%)	1 (11.11%)	2 (20.00%)	0 (0.00%)	2 (22.22%)	9 (9.47%)
Liver function test increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Lymphocyte count decreased	0 (0.00%)	2 (28.57%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	4 (4.21%)
Monocyte count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.05%)
Neutrophil count decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	4 (33.33%)	0 (0.00%)	2 (20.00%)	1 (11.11%)	1 (10.00%)	0 (0.00%)	1 (11.11%)	10 (10.53%)
Neutrophil count increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Platelet count decreased	2 (40.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	2 (16.67%)	1 (10.00%)	1 (11.11%)	2 (20.00%)	1 (10.00%)	0 (0.00%)	10 (10.53%)

Weight decreased	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	0 (0.00%)	1 (10.00%)	2 (22.22%)	7 (7.37%)
Weight increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
White blood cell count decreased	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (25.00%)	0 (0.00%)	1 (11.11%)	3 (30.00%)	0 (0.00%)	1 (11.11%)	9 (9.47%)
Metabolism and nutrition disorders												
Appetite disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Decreased appetite	0 (0.00%)	2 (28.57%)	0 (0.00%)	2 (40.00%)	3 (25.00%)	3 (25.00%)	1 (10.00%)	2 (22.22%)	1 (10.00%)	3 (30.00%)	4 (44.44%)	21 (22.11%)
Dehydration	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	2 (16.67%)	0 (0.00%)	2 (22.22%)	2 (20.00%)	0 (0.00%)	1 (11.11%)	9 (9.47%)
Hypercalcaemia	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 (10.00%)	0 (0.00%)	1 (1.05%)
Hyperglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	2 (20.00%)	0 (0.00%)	2 (20.00%)	1 (10.00%)	0 (0.00%)	6 (6.32%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Hypernatraemia	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 (10.00%)	0 (0.00%)	1 (11.11%)	2 (2.11%)
Hyperphosphataemia	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 (1.05%)
Hypertriglyceridaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Hypoalbuminaemia	1 (20.00%)	2 (28.57%)	0 (0.00%)	1 (20.00%)	3 (25.00%)	4 (33.33%)	2 (20.00%)	4 (44.44%)	4 (40.00%)	1 (10.00%)	1 (11.11%)	23 (24.21%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	1 (11.11%)	2 (20.00%)	0 (0.00%)	0 (0.00%)	5 (5.26%)

Hypoglycaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (16.67%)	2 (16.67%)	2 (20.00%)	2 (22.22%)	1 (10.00%)	0 (0.00%)	2 (22.22%)	12 (12.63%)
Hypomagnesaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (20.00%)	4 (33.33%)	2 (16.67%)	0 (0.00%)	1 (11.11%)	1 (10.00%)	0 (0.00%)	1 (11.11%)	11 (11.58%)
Hyponatraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (11.11%)	5 (5.26%)
Hypophosphataemia	0 (0.00%)	1 (14.29%)	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 (1.05%)
Musculoskeletal and connective tissue disorders												
Arthralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Arthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Back pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	2 (22.22%)	6 (6.32%)
Flank pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (1.05%)
Groin 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%)	1 (11.11%)	1 (1.05%)
Muscle spasms	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Muscle swelling	0 (0.00%)	1 (14.29%)	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 (1.05%)
Muscle tightness	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Muscular weakness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)

Musculoskeletal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
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%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Myalgia	0 (0.00%)	1 (14.29%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (4.21%)
Myositis	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 (1.05%)
Neck pain	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Pain in extremity	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%)	1 (10.00%)	0 (0.00%)	2 (2.11%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												
Pyogenic granuloma	0 (0.00%)	1 (14.29%)	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 (1.05%)
Tumour pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (20.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (4.21%)
Nervous system disorders												
Ataxia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Balance disorder	0 (0.00%)	1 (14.29%)	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 (1.05%)
Dizziness	1 (20.00%)	2 (28.57%)	0 (0.00%)	2 (40.00%)	1 (8.33%)	2 (16.67%)	0 (0.00%)	1 (11.11%)	1 (10.00%)	1 (10.00%)	0 (0.00%)	11 (11.58%)
Dysgeusia	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (20.00%)	1 (8.33%)	0 (0.00%)	2 (20.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (11.11%)	7 (7.37%)

Headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	2 (16.67%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	5 (5.26%)
Hyperaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Hypoaesthesia	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Neuropathy peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	3 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (4.21%)
Paraesthesia	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Peripheral sensory neuropathy	0 (0.00%)	1 (14.29%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.16%)
Seizure	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Somnolence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Taste disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Tongue paralysis	0 (0.00%)	1 (14.29%)	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 (1.05%)
Transient ischaemic attack	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Psychiatric disorders												
Anxiety	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Bruxism	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)

Confusional state	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Depression	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	3 (3.16%)
Insomnia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Mental status changes	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Sleep disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Renal and urinary disorders												
Acute kidney injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Chronic kidney disease	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Dysuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	2 (2.11%)
Haematuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (11.11%)	4 (4.21%)
Hydronephrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Micturition urgency	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Proteinuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	4 (33.33%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (10.00%)	0 (0.00%)	7 (7.37%)
Renal failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Urinary incontinence	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 (1.05%)

Urinary retention	1 (20.00 %)	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 (1.05 %)
Reproductive system and breast disorders												
Benign prostatic hyperplasia	1 (20.00 %)	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 (1.05 %)
Breast pain	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Pelvic pain	0 (0.00%)	1 (14.29 %)	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 (1.05 %)
Scrotal pain	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 (1.05 %)
Uterine pain	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Vulvovaginal pruritus	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 (10.00 %)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Respiratory, thoracic and mediastinal disorders												
Aphonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Cough	1 (20.00 %)	1 (14.29 %)	1 (16.67 %)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	2 (22.22 %)	8 (8.42 %)
Dysphonia	0 (0.00%)	1 (14.29 %)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (10.00 %)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (4.21 %)
Dyspnoea	0 (0.00%)	1 (14.29 %)	2 (33.33 %)	1 (20.00 %)	3 (25.00 %)	1 (8.33%)	2 (20.00 %)	2 (22.22 %)	1 (10.00 %)	1 (10.00 %)	2 (22.22 %)	16 (16.84%)
Dyspnoea at rest	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)

Dyspnoea exertional	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Epistaxis	1 (20.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	4 (4.21%)
Haemoptysis	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Increased upper airway secretion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Nasal congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Oropharyngeal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.16%)
Pharyngeal inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Pleural effusion	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Pleuritic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Pneumonitis	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Productive cough	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	3 (3.16%)
Rhinorrhoea	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 (20.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Sleep apnoea syndrome	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)
Skin and subcutaneous tissue disorders												
Alopecia	0 (0.00%)	1 (14.29%)	1 (16.67%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	2 (22.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (6.32%)

Dermatitis acneiform	2 (40.00 %)	3 (42.86 %)	3 (50.00 %)	1 (20.00 %)	4 (33.33 %)	2 (16.67 %)	3 (30.00 %)	1 (11.11 %)	2 (20.00 %)	2 (20.00 %)	5 (55.56 %)	28 (29.47%)
Dry skin	1 (20.00 %)	1 (14.29 %)	2 (33.33 %)	0 (0.00%)	2 (16.67 %)	4 (33.33 %)	3 (30.00 %)	1 (11.11 %)	0 (0.00%)	1 (10.00 %)	1 (11.11 %)	16 (16.84%)
Eczema asteatotic	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00 %)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	4 (4.21 %)
Hyperhidrosis	0 (0.00%)	1 (14.29 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	3 (3.16 %)
Ingrowing nail	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Night sweats	1 (20.00 %)	1 (14.29 %)	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 (2.11 %)
Pain of skin	0 (0.00%)	1 (14.29 %)	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 (1.05 %)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)
Photosensitivity reaction	0 (0.00%)	0 (0.00%)	1 (16.67 %)	1 (20.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	0 (0.00%)	3 (3.16 %)
Pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67 %)	1 (8.33%)	4 (40.00 %)	2 (22.22 %)	2 (20.00 %)	0 (0.00%)	0 (0.00%)	11 (11.58%)
Rash	0 (0.00%)	3 (42.86 %)	3 (50.00 %)	1 (20.00 %)	8 (66.67 %)	8 (66.67 %)	4 (40.00 %)	5 (55.56 %)	7 (70.00 %)	5 (50.00 %)	1 (11.11 %)	45 (47.37%)
Rash macular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00 %)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11 %)
Rash maculo-papular	0 (0.00%)	1 (14.29 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	2 (20.00 %)	0 (0.00%)	1 (10.00 %)	1 (10.00 %)	0 (0.00%)	6 (6.32 %)
Rash pruritic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.05 %)

Skin burning sensation	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 (1.05%)
Skin fissures	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	4 (4.21%)
Skin necrosis	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 (10.00%)	0 (0.00%)	1 (1.05%)
Urticaria	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Vascular disorders												
Deep vein thrombosis	0 (0.00%)	1 (14.29%)	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 (1.05%)
Embolism	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 (11.11%)	1 (1.05%)
Hypertension	1 (20.00%)	2 (28.57%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	3 (30.00%)	0 (0.00%)	2 (20.00%)	1 (10.00%)	1 (11.11%)	11 (11.58%)
Hypotension	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	3 (3.16%)
Lymphoedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.11%)
Vascular rupture	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 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.05%)

Other Relevant Findings

None

Conclusion:

Based on the totality of the data, MTD was declared as trametinib 1 mg once daily (from Day 1 to 14) in combination with ribociclib 400 mg once daily (from Day 8 to 21) in subjects with metastatic or advanced solid tumors independent of RAS status. The RP2R was declared as trametinib 1 mg once daily (from Day 1 to 14) in combination with ribociclib 300 mg once daily (from Day 8 to 21) in subjects with metastatic or advanced solid tumors independent of RAS status.

The safety and tolerability profile of trametinib plus ribociclib combination observed in the current study was consistent with the known safety profile of each individual compound in an advanced oncology setting.

Date of Clinical Trial Report

12-Jun-2020