NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Trial Indication(s)

metastatic uveal melanoma

Protocol Number

COEB071X2102

Protocol Title

A phase 1 study of AEB071, an oral protein kinase C inhibitor, in patients with metastatic uveal melanoma

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1

Study Start/End Dates

Study Start Date: December 2011 (Actual)
Primary Completion Date: May 2019 (Actual)
Study Completion Date: May 2019 (Actual)

Reason for Termination (If applicable)

Study endpoints were met, lack of efficacy

Study Design/Methodology

Open-label, multicenter, single-agent, Phase I study consisting of a dose escalation part and a dose expansion part

Centers

5 centers in 4 countries: United States(2), Netherlands(1), United Kingdom(1), France(1)

Objectives:

Primary objective(s)

Dose escalation

Estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of sotrastaurin in patients with uveal melanoma

Dose expansion

Characterize the safety and tolerability of the MTD or RDE of sotrastaurin in patients with uveal melanoma and, if warranted, at doses lower than the MTD/RDE

Secondary objectives

Key secondary objectives

Dose escalation

Further characterize the safety and tolerability of sotrastaurin

Dose expansion

Assess preliminary evidence of anti-tumor activity of sotrastaurin in patients with uveal melanoma at the MTD/RDE and, if warranted, at doses lower than the MTD/RDE

Other secondary objectives

- Evaluate the single- and multiple-dose pharmacokinetics (PK) of sotrastaurin and its metabolite AEE800 in patients with uveal melanoma
- Evaluate Gα mutations in uveal melanoma
- Assess the anti-tumor activity at the MTD/RDE (i.e. Progression Free Survival [PFS], Time To Progression)

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

Sotrastaurin tablets were supplied to the Investigators at dose strengths of 50 mg, 100 mg, and 300 mg, and were administered orally. No reference therapy was administered.

Statistical Methods

Methodology: This was an open-label, multicenter, single agent, Phase I study comprised of a dose escalation part and a dose expansion part. The initial sotrastaurin planned dosing was twice daily with the possibility of testing a three times daily dosing schedule, and each cycle was 28 days. An adaptive Bayesian logistic regression model (BLRM) (with 2 parameters) guided by the escalation with overdose control principle was used to make dose recommendations and estimate the MTD during the dose escalation part of the study. The expansion part of the study was to begin once the MTD and/or RDE was determined; the safety of this dose was to be further tested in the expansion part.

Number of subjects (planned and analyzed): Approximately 170 patients were planned to be treated in this study. A total of 153 patients were enrolled prior to early termination. Of these, 113 were in the dose-escalation part (65 in the twice daily dosing schedule and 48 in the three times daily dosing schedule) and 40 were in the dose-expansion part (26 in the twice daily dosing schedule and 14 in the three times daily dosing schedule). As of the data cut-off date of 01-May-2015, 10 patients were still ongoing. The last patient on treatment was transitioned to a Managed Access Program with another protein kinase C (PKC) inhibitor on 24-Apr-2019 due to expiration of the sotrastaurin study treatment.
LPLV occurred on 22-May-2019, the date of the 30-day follow-up visit. The analyses presented in this final CSR were performed after all patients had completed the end-of-study visit.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
• Uveal melanoma with biopsy proven metastatic disease
• Males and females ≥ 18 years of age
• Consent to biopsy of tumor

• Measurable disease according to RECIST version 1.1
• WHO performance status of ≤ 1

Exclusion Criteria:
• Patients with abnormal laboratory values as defined by the protocol
• Patients who are receiving treatment with strong inducers or inhibitors of cytochrome P450 3A4 (CYP3A4) that cannot be discontinued prior to study entry
• Patients with impaired cardiac function or clinically significant cardiac diseases as defined by the protocol
• Patients with another malignancy that was treated within the last three years with the exceptions of localized basal cell carcinoma and cervical carcinoma
• Patients with impairment of gastrointestinal function or disease
• Patients with severe systemic infections
• Patients who are known to be HIV positive and/or have active hepatitis B or C infection
• Time since last therapy for treatment of underlying malignancy:
o Cytotoxic chemotherapy: ≤ duration of the most recent cycle of the previous regimen (a minimum of 2 weeks for all)
o Nitrosurea: ≤ 6 weeks
o Biologic therapy: ≤ 4 weeks
o ≤ 5 x PK half-life of a small molecule therapeutic not otherwise defined above
• Patients having undergone major surgery less than 4 weeks prior to enrollment or have not fully recovered from prior surgery
• Women of child-bearing potential unless they are using highly effective methods of contraception during the dosing and for at least 36 hours after last dose. Highly effective contraception as defined in the protocol.
• Patients with primary central nervous system tumors or brain metastases.
• Pregnant or nursing (lactating) women.

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

300mg BID AEB071	400 mg BID AEB071	450 mg BID AEB071	500 mg BID AEB071	550 mg BID AEB071	600 mg BID AEB071	700 mg BID AEB071	150 mg TID AEB071	200 mg TID AEB071	250/200/ 250 mg TID AEB071	250 mg TID AEB071	300/250/ 250 mg TID AEB071	300 mg TID AEB071	Total

Arm/Group Description	escalation	escalation	escalation	escalation	escalation	escalation and expansion	escalation and expansion	escalation	escalation	escalation	escalation and expansion	escalation	escalation	
Started	6	12	5	6	18	15	29	6	6	6	26	11	7	153
Completed	6	10	5	5	15	10	21	6	6	6	19	11	2	122
Not Completed	0	2	0	1	3	5	8	0	0	0	7	0	5	31
administrative problems	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Withdrawal by Subject	0	0	0	0	0	3	2	0	0	0	2	0	3	10
Adverse Event	0	2	0	1	3	2	6	0	0	0	4	0	2	20

Baseline Characteristics

	300mg BID AEB071	400 mg BID AEB071	450 mg BID AEB071	500 mg BID AEB071	550 mg BID AEB071	600 mg BID AEB071	700 mg BID AEB071	150 mg TID AEB071	200 mg TID AEB071	250/200/250 mg TID AEB071	250 mg TID AEB071	300/250/250 mg TID AEB071	300 mg TID AEB071	Total
Arm/Group Description	escalation	escalation	escalation	escalation	escalation	escalation and expansion	escalation and expansion	escalation	escalation	escalation	escalation and expansion	escalation	escalation	
Number of Participants [units:	6	12	5	6	18	15	29	6	6	6	26	11	7	153

participants]														
Age Continuous (units: years) Mean ± Standard Deviation														
	56.2±12.24	54.1±14.65	51.6±24.47	46.2±14.80	60.8±9.95	57.2±12.71	56.0±13.09	54.7±15.81	53.7±16.73	62.2±11.99	57.9±11.59	60.0±12.51	57.4±15.22	56.8±13.24
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)														
Female	3	8	2	5	10	9	18	4	3	3	12	5	5	87
Male	3	4	3	1	8	6	11	2	3	3	14	6	2	66
Race/Ethnicity, Customized[1] (units: participants) Count of Participants (Not Applicable)														
Caucasian	6	12	4	6	16	12	29	6	6	6	23	10	7	143
other	0	0	1	0	2	3	0	0	0	0	3	1	0	10

[1] Race

Summary of Efficacy

Primary Outcome Result(s)

Incidence of dose limiting toxicities (DLT) during the first cycle of treatment

(Time Frame: up to 28 days)

300mg BID AEB071	400 mg BID AEB071	450 mg BID AEB071	500 mg BID AEB071	550 mg BID AEB071	600 mg BID AEB071	700 mg BID AEB071	150 mg TID AEB071	200 mg TID AEB071	250/200/250 mg TID AEB071	250 mg TID AEB071	300/250/250 mg TID AEB071	300 mg TID AEB071

Arm/Group Description	escalation	escalation	escalation	escalation	escalation	escalation and expansion	escalation and expansion	escalation	escalation	escalation	escalation and expansion	escalation	escalation
Number of Participants Analyzed [units: participants]	6	12	5	6	18	15	29	6	6	6	26	11	7
Incidence of dose limiting toxicities (DLT) during the first cycle of treatment (units: participants) Count of Participants (Not Applicable)													
	0 (%)	1 (9.09%)	0 (%)	2 (33.33%)	2 (11.76%)	0 (%)	3 (25%)	0 (%)	0 (%)	1 (16.67%)	0 (%)	0 (%)	4 (80%)

Secondary Outcome Result(s)

Overall response rate (Complete Response (CR) + Partial Response(PR)) to AEB071 using RECIST version 1.1

(Time Frame: Baseline, 12 months)

	300mg BID AEB071	400 mg BID AEB071	450 mg BID AEB071	500 mg BID AEB071	550 mg BID AEB071	600 mg BID AEB071	700 mg BID AEB071	150 mg TID AEB071	200 mg TID AEB071	250/200/250 mg TID AEB071	250 mg TID AEB071	300/250/250 mg TID AEB071	300 mg TID AEB071
Arm/Group Description	escalation	escalation	escalation	escalation	escalation	escalation and expansion	escalation and expansion	escalation	escalation	escalation	escalation and expansion	escalation	escalation
Number of Participants Analyzed [units: participants]	6	12	5	6	18	15	29	6	6	6	26	11	7
Overall response rate (Complete Response (CR) + Partial Response(PR)) to AEB071 using RECIST version 1.1 (units: participants) Count of Participants (Not Applicable)													
CR or PR	0 (%)	0 (%)	0 (%)	1 (16.67%)	0 (%)	1 (6.67%)	1 (3.45%)	0 (%)	0 (%)	0 (%)	1 (3.85%)	0 (%)	0 (%)

Time to progression using RECIST version 1.1

(Time Frame: 6 months, 12 months)

	300mg BID AEB071	400 mg BID AEB071	450 mg BID AEB071	500 mg BID AEB071	550 mg BID AEB071	600 mg BID AEB071	700 mg BID AEB071	150 mg TID AEB071	200 mg TID AEB071	250/200/250 mg TID AEB071	250 mg TID AEB071	300/250/250 mg TID AEB071	300 mg TID AEB071
Arm/Group Description	escalation	escalation	escalation	escalation	escalation	escalation and expansion	escalation and expansion	escalation	escalation	escalation	escalation and expansion	escalation	escalation
Number of Participants Analyzed [units: participants]	6	12	5	6	18	15	29	6	6	6	26	11	7
Time to progression using RECIST version 1.1 (units: percentage) Mean (95% Confidence Interval)													
6 months	16.7 (0.0 to 46.5)	27.5 (1.0 to 54.0)	0.0 (0.0 to 0.0)	60.0 (17.1 to 100.0)	31.7 (8.8 to 54.5)	15.4 (0.0 to 35.0)	31.9 (12.7 to 51.1)	20.0 (0.0 to 55.1)	0.0 (0.0 to 0.0)	40.0 (0.0 to 82.9)	18.4 (2.3 to 34.5)	34.3 (3.1 to 65.5)	0.0 (0.0 to 0.0)
12 months	0.0 (0.0 to 0.0)	9.2 (0.0 to 26.3)	0.0 (0.0 to 0.0)	20.0 (0.0 to 55.1)	6.3 (0.0 to 18.3)	0.0 (0.0 to 0.0)	18.2 (2.2 to 34.3)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	9.2 (0.0 to 21.3)	22.9 (0.0 to 50.6)	0.0 (0.0 to 0.0)

Progression free survival using RECIST version 1.1

(Time Frame: 6 months, 12 months)

	300mg BID AEB071	400 mg BID AEB071	450 mg BID AEB071	500 mg BID AEB071	550 mg BID AEB071	600 mg BID AEB071	700 mg BID AEB071	150 mg TID AEB071	200 mg TID AEB071	250/200/250 mg TID AEB071	250 mg TID AEB071	300/250/250 mg TID AEB071	300 mg TID AEB071
Arm/Group Description	escalation	escalation	escalation	escalation	escalation	escalation and expansion	escalation and expansion	escalation	escalation	escalation	escalation and expansion	escalation	escalation

Number of Participants Analyzed [units: participants]	6	12	5	6	18	15	29	6	6	6	26	11	7
Progression free survival using RECIST version 1.1 (units: percentage) Mean (95% Confidence Interval)													
6 months	16.7 (0.0 to 46.5)	25.0 (0.5 to 49.5)	0.0 (0.0 to 0.0)	60.0 (17.1 to 100.0)	31.7 (8.8 to 54.5)	9.6 (0.0 to 27.2)	31.9 (12.7 to 51.1)	20.0 (0.0 to 55.1)	0.0 (0.0 to 0.0)	40.0 (0.0 to 82.9)	18.4 (2.3 to 34.5)	34.3 (3.1 to 65.5)	0.0 (0.0 to 0.0)
12 months	0.0 (0.0 to 0.0)	8.3 (0.0 to 24.0)	0.0 (0.0 to 0.0)	20.0 (0.0 to 55.1)	6.3 (0.0 to 18.3)	0.0 (0.0 to 0.0)	18.2 (2.2 to 34.3)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	9.2 (0.0 to 21.3)	22.9 (0.0 to 50.6)	0.0 (0.0 to 0.0)

AEB071/AEE800 pharmacokinetic parameters (AUC0-8h, Cmax)

(Time Frame: Day1, Day 8)

	300mg BID AEB071	**400 mg BID AEB071**	**450 mg BID AEB071**	**500 mg BID AEB071**	**550 mg BID AEB071**	**600 mg BID AEB071**	**700 mg BID AEB071**	**150 mg TID AEB071**	**200 mg TID AEB071**	**250/200/250 mg TID AEB071**	**250 mg TID AEB071**	**300/250/250 mg TID AEB071**	**300 mg TID AEB071**
Arm/Group Description	escalation	escalation	escalation	escalation	escalation	escalation and expansion	escalation and expansion	escalation	escalation	escalation	escalation and expansion	escalation	escalation
Number of Participants Analyzed [units: participants]	6	12	4	6	17	13	24	6	5	6	25	10	7

AEB071/AEE800 pharmacokinetic parameters (AUC0-8h, Cmax)
(units: h*ng/ml; ng/ ml;)
Geometric Mean (Geometric Coefficient of Variation)

AUC 0-8h (h*ng/ml) day 1	16700 (27.7%)	13900 (53.9%)	13000 (12.0%)	17000 (49.2%)	22300 (44.9%)	19700 (56.4%)	21800 (53.3%)	7170 (33.1%)	8500 (43.5%)	14300 (62.6%)	11600 (52.6%)	10800 (77.6%)	14000 (87.1%)
Cmax (ng/ml) day 1	3650 (33.4%)	2970 (69.4%)	2660 (4.23%)	4140 (57.4%)	4300 (47.8%)	3700 (35.1%)	4880 (39.3%)	1910 (53.0%)	1880 (69.2%)	2900 (54.7%)	2500 (53.7%)	2690 (65.6%)	3070 (60.8%)
AUC 0-8h (h*ng/ml) day 8	19200 (20.4%)	19100 (35%)	20400 (23.8%)	25000 (30.4%)	30200 (33.7%)	24700 (43.5%)	32900 (30.3%)	9480 (33.3%)	12600 (63.1%)	15500 (27.7%)	15800 (59.6%)	10900 (78.0%)	36800 (69.5%)
Cmax (ng/ml) day 8	3950 (12.4%)	3850 (41.2%)	3890 (14.1%)	4890 (17.4%)	5740 (40.4%)	4680 (45.9%)	5980 (35.7%)	2250 (55.9%)	2610 (52.5%)	3280 (28.5%)	3560 (63.8%)	2410 (64.3%)	6770 (56.7%)

AEB071/AEE800 pharmacokinetic parameters (Tmax)

(Time Frame: Day1, Day 8)

	300mg BID AEB071	400 mg BID AEB071	450 mg BID AEB071	500 mg BID AEB071	550 mg BID AEB071	600 mg BID AEB071	700 mg BID AEB071	150 mg TID AEB071	200 mg TID AEB071	250/200/250 mg TID AEB071	250 mg TID AEB071	300/250/250 mg TID AEB071	300 mg TID AEB071
Arm/Group Description	escalation	escalation	escalation	escalation	escalation	escalation and expansion	escalation and expansion	escalation	escalation	escalation	escalation and expansion	escalation	escalation
Number of Participants Analyzed [units: participants]	6	12	4	6	17	13	24	6	5	6	25	10	7

AEB071/AEE800 pharmacokinetic parameters (Tmax)
(units: hours)
Median (Full Range)

day 1	1.50 (0.5 to 4.17)	3.83 (0.5 to 5.62)	2.44 (0.5 to 4.17)	0.950 (0.5 to 4.10)	4.61 (0.917 to 7.08)	1.95 (0.5 to 4.17)	3.63 (1.0 to 6.12)	2.0 (1.0 to 4.0)	2.17 (0.5 to 4.0)	3.0 (1.0 to 4.2)	1.44 (0.5 to 4.43)	4.0 (0.5 to 6.0)	4.0 (1.0 to 6.0)
day 8	1.02 (0.944 to 1.67)	1.36 (0.771 to 3.29)	2.03 (1.78 to 3.55)	2.10 (1.0 to 2.25)	2.28 (0 to 6.67)	2.08 (0.5 to 5.28)	3.67 (1.0 to 4.28)	1.08 (0.5 to 4.0)	2.0 (0.833 to 4.0)	1.93 (1.0 to 4.0)	1.0 (0.533 to 4.03)	3.67 (0.833 to 6.0)	2.07 (1.17 to 2.08)

Gα genotype in tumor specimens - summary of somatic alterations

(Time Frame: Baseline, 28 days)

	300mg BID AEB071	**400 mg BID AEB071**	**450 mg BID AEB071**	**500 mg BID AEB071**	**550 mg BID AEB071**	**600 mg BID AEB071**	**700 mg BID AEB071**	**150 mg TID AEB071**	**250/200/250 mg TID AEB071**	**200 mg TID AEB071**	**250 mg TID AEB071**	**300/250/250 mg TID AEB071**	**300 mg TID AEB071**
Arm/Group Description	escalation	escalation	escalation	escalation	escalation	escalation and expansion	escalation and expansion	escalation	escalation	escalation	escalation and expansion	escalation	escalation
Number of Participants Analyzed [units: participants]	6	12	5	6	18	15	29	6	6	6	26	11	7
Gα genotype in tumor specimens - summary of somatic alterations (units: participants) Count of Participants (Not Applicable)													
GNAQ	1 (50%)	4 (57.14%)	3 (60%)	2 (50%)	8 (66.67%)	2 (50%)	9 (69.23%)	4 (66.67%)	4 (66.67%)	2 (66.67%)	9 (60%)	1 (12.5%)	2 (50%)
GNA11	1 (50%)	3 (42.86%)	2 (40%)	2 (50%)	2 (16.67%)	2 (50%)	3 (23.08%)	1 (16.67%)	2 (33.33%)	1 (33.33%)	5 (33.33%)	6 (75%)	2 (50%)

BAP1	1 (50%)	4 (57.14%)	3 (60%)	3 (75%)	6 (50%)	1 (25%)	8 (61.54%)	1 (16.67%)	5 (83.33%)	0 (%)	8 (53.33%)	4 (50%)	4 (100%)
SF3B1	1 (50%)	2 (28.57%)	1 (20%)	0 (%)	3 (25%)	1 (25%)	3 (23.08%)	2 (33.33%)	0 (%)	2 (66.67%)	3 (20%)	1 (12.5%)	1 (25%)
MYC	0 (%)	1 (14.29%)	3 (60%)	1 (25%)	0 (%)	0 (%)	5 (38.46%)	1 (16.67%)	0 (%)	0 (%)	6 (40%)	3 (37.5%)	0 (%)

Summary of Safety

Safety Results

All-Cause Mortality

	AEB071@300 mg (BID) N = 6	**AEB071@400 mg (BID) N = 12**	**AEB071@450 mg (BID) N = 5**	**AEB071@500 mg (BID) N = 6**	**AEB071@550 mg (BID) N = 18**	**AEB071@600 mg (BID) N = 15**	**AEB071@700 mg (BID) N = 29**	**All@patients@(BID) N = 91**	**AEB071@150 mg (TID) N = 6**	**AEB071@200 mg (TID) N = 6**	**AEB071@250/200/250 mg (TID) N = 6**	**AEB071@250 mg (TID) N = 26**	**AEB071@300/250/250 mg (TID) N = 11**	**AEB071@300 mg (TID) N = 7**	**All@patients@(TID) N = 62**	**All@patients N = 153**
Arm/Group Description	AEB071@300 mg (BID)	AEB071@400 mg (BID)	AEB071@450 mg (BID)	AEB071@500 mg (BID)	AEB071@550 mg (BID)	AEB071@600 mg (BID)	AEB071@700 mg (BID)	All@patients@(BID)	AEB071@150 mg (TID)	AEB071@200 mg (TID)	AEB071@250/200/250 mg (TID)	AEB071@250 mg (TID)	AEB071@300/250/250 mg (TID)	AEB071@300 mg (TID)	All@patients@(TID)	All@patients
Total participants	0 (0.00%)	3 (25.00%)	2 (40.00%)	0 (0.00%)	2 (11.11%)	1 (6.67%)	5 (17.24%)	13 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (11.54%)	0 (0.00%)	0 (0.00%)	3 (4.84%)	16 (10.46%)

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Serious Adverse Events by System Organ Class

Time Frame	8 years
Additional Description	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment

	AEB071@300 mg (BID) N = 6	AEB071@400 mg (BID) N = 12	AEB071@450 mg (BID) N = 5	AEB071@500 mg (BID) N = 6	AEB071@550 mg (BID) N = 18	AEB071@600 mg (BID) N = 15	AEB071@700 mg (BID) N = 29	All@patients@(BID) N = 91	AEB071@150 mg (TID) N = 6	AEB071@200 mg (TID) N = 6	AEB071@250/200/250 mg (TID) N = 6	AEB071@250 mg (TID) N = 26	AEB071@300/250/250 mg (TID) N = 11	AEB071@300 mg (TID) N = 7	All@patients@(TID) N = 62	All@patients N = 153
Arm/Group Description	AEB071@300 mg (BID)	AEB071@400 mg (BID)	AEB071@450 mg (BID)	AEB071@500 mg (BID)	AEB071@550 mg (BID)	AEB071@600 mg (BID)	AEB071@700 mg (BID)	All@patients@(BID)	AEB071@150 mg (TID)	AEB071@200 mg (TID)	AEB071@250/200/250 mg (TID)	AEB071@250 mg (TID)	AEB071@300/250/250 mg (TID)	AEB071@300 mg (TID)	All@patients@(TID)	All@patients
Total participants affected	1 (16.67%)	5 (41.67%)	2 (40.00%)	1 (16.67%)	7 (38.89%)	4 (26.67%)	10 (34.48%)	30 (32.97%)	2 (33.33%)	3 (50.00%)	1 (16.67%)	6 (23.08%)	4 (36.36%)	4 (57.14%)	20 (32.26%)	50 (32.68%)
Blood and lymphatic system																

disorders															
Anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (6.67%)	1 (3.45%)	3 (3.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.96%)
Cardiac disorders															
Myocardial infarction	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%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (0.65%)
Pericardial effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (3.45%)	2 (2.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.31%)
Gastrointestinal disorders															
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	2 (1.31%)
Abdominal pain upper	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Ascites	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Constipation	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (3.85%)	0 (0.00%)	1 (1.61%)	1 (0.65%)
Diarrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Dysphagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (3.85%)	0 (0.00%)	1 (1.61%)	1 (0.65%)

Gastrooesophageal reflux disease	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Haematemesis	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	1 (9.09%)	1 (14. 29%)	3 (4.84 %)	5 (3. 27%)
Nausea	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	2 (11. 11%)	0 (0.0 0%)	0 (0.0 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	5 (3. 27%)
Peritoneal haemorrhage	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Small intestinal obstruction	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Upper gastrointestinal haemorrhage	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Vomiting	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	4 (22. 22%)	0 (0.0 0%)	1 (3.4 5%)	5 (5.49 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	7 (4. 58%)
General disorders and administration site																

conditions																
Fatigue	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
General physical health deterioration	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Oedema peripheral	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Pyrexia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	1 (1.10 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	2 (1. 31%)
Hepatobiliary disorders																
Budd-Chiari syndrome	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Hepatic mass	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Infections and infestations																
Gastroenteritis	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	2 (1. 31%)

Pneumonia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Pyelonephritis	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Upper respiratory tract infection	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Injury, poisoning and procedural complications																
Contusion	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Joint dislocation	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Lower limb fracture	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	1 (16. 67%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Post procedural bile leak	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Post procedural haematoma	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)

Procedural pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Spinal compression fracture	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Investigations																
Blood bilirubin increased	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Musculoskeletal and connective tissue disorders																
Neck pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (14. 29%)	1 (1.61 %)	1 (0. 65%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)																
Malignant	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)

melanoma																
Nervous system disorders																
Neuralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	2 (1.31%)
Seizure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (1.61%)	1 (0.65%)
Spinal cord compression	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (1.61%)	1 (0.65%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (9.09%)	0 (0.00%)	1 (1.61%)	1 (0.65%)
Psychiatric disorders																
Depression	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Renal and urinary disorders																
Acute kidney injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Haematuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (9.09%)	0 (0.00%)	1 (1.61%)	1 (0.65%)

Nephrolithiasis	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Urinary retention	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (1.61%)	1 (0.65%)
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%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (0.65%)
Pulmonary embolism	1 (16.67%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	3 (3.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.96%)
Respiratory failure	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Skin and subcutaneous tissue disorders																
Dermatitis exfoliative 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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (0.65%)

Rash	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Skin toxicit y	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Social circums tances																
Physic al disabil ity	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Vascula r disorde rs																
Hypot ension	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	2 (1. 31%)
Venou s throm bosis	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)

Other Adverse Events by System Organ Class

Time Frame	8 years
Additional Description	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	AEB071 @300 mg (BID) N = 6	AEB071 @400 mg (BID) N = 12	AEB071 @450 mg (BID) N = 5	AEB071 @500 mg (BID) N = 6	AEB071 @550 mg (BID) N = 18	AEB071 @600 mg (BID) N = 15	AEB071 @700 mg (BID) N = 29	All@patients@(BID) N = 91	AEB071 @150 mg (TID) N = 6	AEB071 @200 mg (TID) N = 6	AEB071 @250/200/250 mg (TID) N = 6	AEB071 @250 mg (TID) N = 26	AEB071 @300/250/250 mg (TID) N = 11	AEB071 @300 mg (TID) N = 7	All@patients@(TID) N = 62	All@patients N = 153
Arm/Group Description	AEB071@300 mg (BID)	AEB071@400 mg (BID)	AEB071@450 mg (BID)	AEB071@500 mg (BID)	AEB071@550 mg (BID)	AEB071@600 mg (BID)	AEB071@700 mg (BID)	All@patients@(BID)	AEB071@150 mg (TID)	AEB071@200 mg (TID)	AEB071@250/200/250 mg (TID)	AEB071@250 mg (TID)	AEB071@300/250/250 mg (TID)	AEB071@300 mg (TID)	All@patients@(TID)	All@patients
Total participants affected	6 (100.00%)	11 (91.67%)	5 (100.00%)	6 (100.00%)	18 (100.00%)	15 (100.00%)	29 (100.00%)	90 (98.90%)	6 (100.00%)	6 (100.00%)	6 (100.0 0%)	26 (100.00%)	11 (100.00%)	7 (100.00%)	62 (100.00%)	152 (99.35%)
Blood and lymphatic system disorders																
Anaemia	2 (33.33%)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67%)	3 (16.67%)	4 (26.67%)	4 (13.79%)	14 (15.38%)	0 (0.0 0%)	1 (16.67%)	2 (33.33%)	1 (3.85%)	1 (9.09%)	3 (42.86%)	8 (12.90%)	22 (14.38%)
Leukopenia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (7.69%)	0 (0.00%)	0 (0.0 0%)	2 (3.23%)	2 (1.31%)
Lymphopenia	0 (0.0 0%)	2 (16.67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	0 (0.0 0%)	1 (1.61%)	3 (1.96%)
Thrombocytopenia	0 (0.0 0%)	1 (8.33%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (13.33%)	1 (3.45%)	4 (4.40%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	1 (14.29%)	2 (3.23%)	6 (3.92%)
Cardiac disorders																

Palpitations	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	2 (13.33%)	3 (10.34%)	7 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	8 (5.23%)
Sinus tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.85%)	0 (0.00%)	0 (0.00%)	2 (3.23%)	2 (1.31%)
Tachycardia	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	2 (13.33%)	2 (6.90%)	6 (6.59%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (11.54%)	0 (0.00%)	0 (0.00%)	3 (4.84%)	9 (5.88%)
Ear and labyrinth disorders																
Deafness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Hypoacusis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Tinnitus	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Vertigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (1.61%)	2 (1.31%)
Eye disorders																
Blepharitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	2 (1.31%)
Dyschromatopsia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Eye disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Ocular hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (9.09%)	0 (0.00%)	1 (1.61%)	1 (0.65%)

Photopsia	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	1 (16. 67%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	4 (2. 61%)
Vision blurred	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	2 (6.9 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	3 (1. 96%)
Visual impairment	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	1 (5.5 6%)	0 (0.0 0%)	1 (3.4 5%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	4 (2. 61%)
Gastrointestinal disorders																
Abdominal discomfort	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Abdominal distension	0 (0.0 0%)	2 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	1 (6.6 7%)	0 (0.0 0%)	4 (4.40 %)	1 (16. 67%)	1 (16. 67%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	6 (3. 92%)
Abdominal pain	2 (33. 33%)	0 (0.0 0%)	1 (20. 00%)	1 (16. 67%)	1 (5.5 6%)	3 (20. 00%)	2 (6.9 0%)	10 (10.9 9%)	3 (50. 00%)	2 (33. 33%)	1 (16.67 %)	2 (7.6 9%)	1 (9.09%)	1 (14. 29%)	10 (16.1 3%)	20 (1 3.07 %)
Abdominal pain upper	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	2 (11. 11%)	2 (13. 33%)	3 (10. 34%)	8 (8.79 %)	0 (0.0 0%)	1 (16. 67%)	1 (16.67 %)	1 (3.8 5%)	2 (18.18 %)	1 (14. 29%)	6 (9.68 %)	14 (9 .15%)
Abdominal tenderness	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Anal incontinence	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Aphthous ulcer	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	3 (1. 96%)

Ascites	0 (0.0 0%)	2 (16. 67%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	4 (4.40 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	4 (2. 61%)
Colitis	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	2 (1. 31%)
Constip ation	3 (50. 00%)	6 (50. 00%)	3 (60. 00%)	5 (83. 33%)	12 (6 6.67 %)	9 (60. 00%)	18 (6 2.07 %)	56 (61.5 4%)	5 (83. 33%)	2 (33. 33%)	5 (83.33 %)	22 (8 4.62 %)	7 (63.64 %)	2 (28. 57%)	43 (69.3 5%)	99 (6 4.71 %)
Diarrho ea	1 (16. 67%)	4 (33. 33%)	1 (20. 00%)	4 (66. 67%)	12 (6 6.67 %)	8 (53. 33%)	17 (5 8.62 %)	47 (51.6 5%)	2 (33. 33%)	2 (33. 33%)	1 (16.67 %)	11 (4 2.31 %)	8 (72.73 %)	2 (28. 57%)	26 (41.9 4%)	73 (4 7.71 %)
Dry mouth	0 (0.0 0%)	1 (8.3 3%)	1 (20. 00%)	0 (0.0 0%)	1 (5.5 6%)	2 (13. 33%)	0 (0.0 0%)	5 (5.49 %)	0 (0.0 0%)	1 (16. 67%)	0 (0.00%)	3 (11. 54%)	0 (0.00%)	0 (0.0 0%)	4 (6.45 %)	9 (5. 88%)
Dyspep sia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (11. 11%)	1 (6.6 7%)	7 (24. 14%)	10 (10.9 9%)	0 (0.0 0%)	1 (16. 67%)	0 (0.00%)	2 (7.6 9%)	1 (9.09%)	0 (0.0 0%)	4 (6.45 %)	14 (9 .15%)
Eructati on	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Flatule nce	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	2 (1. 31%)
Gastric ulcer	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Gastroi ntestina l disorde r	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	2 (1. 31%)
Gastroi ntestina l motility disorde r	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	1 (9.09%)	0 (0.0 0%)	2 (3.23 %)	4 (2. 61%)
Gastro oesoph ageal	0 (0.0 0%)	2 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	1 (6.6 7%)	2 (6.9 0%)	6 (6.59 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (7.6 9%)	1 (9.09%)	0 (0.0 0%)	3 (4.84 %)	9 (5. 88%)

reflux disease																
Gingival bleeding	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	2 (1. 31%)
Gingival pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Haematemesis	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Haematochezia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Haemorrhoidal haemorrhage	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Haemorrhoids	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	1 (3.4 5%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	4 (2. 61%)
Melaena	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Mouth ulceration	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (33. 33%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	3 (1. 96%)
Nausea	2 (33. 33%)	8 (66. 67%)	5 (10 0.00 %)	6 (10 0.00 %)	17 (9 4.44 %)	14 (9 3.33 %)	28 (9 6.55 %)	80 (87.9 1%)	4 (66. 67%)	5 (83. 33%)	4 (66.67 %)	21 (8 0.77 %)	8 (72.73 %)	7 (10 0.00 %)	49 (79.0 3%)	129 (84.3 1%)
Oesophageal irritation	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Oesophagitis	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Rectal haemorrhage	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)

Retching	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (14. 29%)	1 (1.61 %)	1 (0. 65%)
Stomatitis	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	1 (16. 67%)	1 (5.5 6%)	1 (6.6 7%)	0 (0.0 0%)	4 (4.40 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	5 (3. 27%)
Swollen tongue	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Vomiting	1 (16. 67%)	7 (58. 33%)	3 (60. 00%)	5 (83. 33%)	10 (5 5.56 %)	11 (7 3.33 %)	24 (8 2.76 %)	61 (67.0 3%)	2 (33. 33%)	3 (50. 00%)	3 (50.00 %)	11 (4 2.31 %)	7 (63.64 %)	6 (85. 71%)	32 (51.6 1%)	93 (6 0.78 %)
General disorders and administration site conditions																
Asthenia	1 (16. 67%)	2 (16. 67%)	5 (10 0.00 %)	2 (33. 33%)	6 (33. 33%)	5 (33. 33%)	10 (3 4.48 %)	31 (34.0 7%)	1 (16. 67%)	1 (16. 67%)	1 (16.67 %)	11 (4 2.31 %)	4 (36.36 %)	1 (14. 29%)	19 (30.6 5%)	50 (3 2.68 %)
Chills	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	1 (3.4 5%)	2 (2.20 %)	1 (16. 67%)	1 (16. 67%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	1 (14. 29%)	4 (6.45 %)	6 (3. 92%)
Fatigue	0 (0.0 0%)	5 (41. 67%)	0 (0.0 0%)	2 (33. 33%)	10 (5 5.56 %)	5 (33. 33%)	11 (3 7.93 %)	33 (36.2 6%)	4 (66. 67%)	1 (16. 67%)	4 (66.67 %)	11 (4 2.31 %)	3 (27.27 %)	3 (42. 86%)	26 (41.9 4%)	59 (3 8.56 %)
Feeling abnormal	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Feeling hot	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Hypothermia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Malaise	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (6.9 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	3 (1. 96%)
Mucosal	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	1 (16. 67%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	1 (9.09%)	0 (0.0 0%)	2 (3.23 %)	5 (3. 27%)

inflammation																
Non-cardiac chest pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	1 (6.6 7%)	3 (10. 34%)	5 (5.49 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	5 (3. 27%)
Oedema peripheral	0 (0.0 0%)	2 (16. 67%)	1 (20. 00%)	1 (16. 67%)	0 (0.0 0%)	1 (6.6 7%)	1 (3.4 5%)	6 (6.59 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (7.6 9%)	1 (9.09%)	0 (0.0 0%)	3 (4.84 %)	9 (5. 88%)
Peripheral swelling	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Pyrexia	0 (0.0 0%)	1 (8.3 3%)	1 (20. 00%)	0 (0.0 0%)	4 (22. 22%)	0 (0.0 0%)	1 (3.4 5%)	7 (7.69 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	1 (3.8 5%)	1 (9.09%)	1 (14. 29%)	4 (6.45 %)	11 (7 .19%)
Swelling	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Xerosis	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Hepatobiliary disorders																
Cholestasis	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	2 (1. 31%)
Hepatic pain	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	1 (16. 67%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	4 (2. 61%)
Hepatocellular injury	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	2 (1. 31%)
Hepatomegaly	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)

Immune system disorders																
Contrast media allergy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	1 (3.45%)	3 (3.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.96%)
Infections and infestations																
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Candida infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Cystitis	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	1 (14.29%)	2 (3.23%)	3 (1.96%)
Ear 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%)	0 (0.00%)	2 (7.69%)	1 (9.09%)	0 (0.00%)	3 (4.84%)	3 (1.96%)
Eye infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	2 (2.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.31%)
Folliculitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Fungal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	2 (1.31%)
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 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (0.65%)

Gastroenteritis	0 (0.00%)	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%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (0.65%)
Gastrointestinal candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Influenza	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.45%)	2 (2.20%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	3 (1.96%)
Localised infection	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Lung infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (1.61%)	2 (1.31%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	3 (3.30%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	4 (2.61%)
Ophthalmic herpes zoster	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Oral candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Oral herpes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
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%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (0.65%)
Respiratory	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)

tract infection																
Staphylococcal infection	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Tonsillitis	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Tooth infection	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Upper respiratory tract infection	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	2 (1. 31%)
Urinary tract infection	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (11. 11%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	2 (18.18 %)	0 (0.0 0%)	3 (4.84 %)	5 (3. 27%)
Injury, poisoning and procedural complications																
Contusion	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	1 (3.4 5%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	3 (1. 96%)
Procedural dizziness	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Investigations																

Alanine aminotransferase increased	2 (33.33%)	3 (25.00%)	0 (0.0 0%)	3 (50.00%)	2 (11.11%)	2 (13.33%)	3 (10.34%)	15 (16.48%)	0 (0.0 0%)	1 (16.67%)	2 (33.33%)	3 (11.54%)	0 (0.00%)	1 (14.29%)	7 (11.29%)	22 (14.38%)
Aspartate aminotransferase increased	2 (33.33%)	5 (41.67%)	0 (0.0 0%)	1 (16.67%)	3 (16.67%)	2 (13.33%)	3 (10.34%)	16 (17.58%)	1 (16.67%)	1 (16.67%)	2 (33.33%)	4 (15.38%)	0 (0.00%)	1 (14.29%)	9 (14.52%)	25 (16.34%)
Blood alkaline phosphatase increased	0 (0.0 0%)	2 (16.67%)	0 (0.0 0%)	1 (16.67%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.45%)	4 (4.40%)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67%)	2 (7.69%)	0 (0.00%)	0 (0.0 0%)	3 (4.84%)	7 (4.58%)
Blood bilirubin increased	2 (33.33%)	1 (8.33%)	1 (20.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	4 (4.40%)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67%)	1 (3.85%)	0 (0.00%)	0 (0.0 0%)	2 (3.23%)	6 (3.92%)
Blood bilirubin unconjugated increased	1 (16.67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (0.65%)
Blood calcium decreased	0 (0.0 0%)	1 (8.33%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (0.65%)
Blood creatinine increased	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.56%)	2 (13.33%)	3 (10.34%)	6 (6.59%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	6 (3.92%)

Blood lactate dehydrogenase increased	1 (16.67%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.31%)
Blood magnesium decreased	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Blood pressure decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)
Electrocardiogram QT prolonged	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.85%)	0 (0.00%)	0 (0.00%)	2 (3.23%)	3 (1.96%)
Gamma-glutamyltransferase increased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	3 (3.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.69%)	0 (0.00%)	0 (0.00%)	2 (3.23%)	5 (3.27%)
Haemoglobin decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	0 (0.00%)	2 (3.23%)	3 (1.96%)
Neutrophil count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (1.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.65%)

Platelet count decreased	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Urine analysis abnormal	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Weight decreased	1 (16. 67%)	3 (25. 00%)	3 (60. 00%)	3 (50. 00%)	8 (44. 44%)	6 (40. 00%)	15 (5 1.72 %)	39 (42.8 6%)	1 (16. 67%)	1 (16. 67%)	1 (16.67 %)	5 (19. 23%)	4 (36.36 %)	3 (42. 86%)	15 (24.1 9%)	54 (3 5.29 %)
Weight increased	0 (0.0 0%)	2 (16. 67%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	4 (15. 38%)	2 (18.18 %)	0 (0.0 0%)	6 (9.68 %)	9 (5. 88%)
White blood cell count decreased	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Metabolism and nutrition disorders																
Appetite disorder	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	2 (11. 11%)	0 (0.0 0%)	0 (0.0 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (7.6 9%)	1 (9.09%)	0 (0.0 0%)	3 (4.84 %)	6 (3. 92%)
Decreased appetite	1 (16. 67%)	2 (16. 67%)	3 (60. 00%)	4 (66. 67%)	5 (27. 78%)	7 (46. 67%)	11 (3 7.93 %)	33 (36.2 6%)	1 (16. 67%)	2 (33. 33%)	2 (33.33 %)	8 (30. 77%)	4 (36.36 %)	3 (42. 86%)	20 (32.2 6%)	53 (3 4.64 %)
Dehydration	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	3 (10. 34%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	4 (2. 61%)

Diabetes mellitus	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	1 (16. 67%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Gout	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	1 (16. 67%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Hypercholesterolaemia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Hyperglycaemia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Hyperkalaemia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	2 (13. 33%)	0 (0.0 0%)	3 (3.30 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	2 (3.23 %)	5 (3. 27%)
Hypoalbuminaemia	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	4 (2. 61%)
Hypocalcaemia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	3 (1. 96%)
Hypokalaemia	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	2 (1. 31%)
Hyponatraemia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	2 (1. 31%)
Hypophosphataemia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (16. 67%)	0 (0.0 0%)	1 (16.67 %)	2 (7.6 9%)	1 (9.09%)	0 (0.0 0%)	5 (8.06 %)	5 (3. 27%)
Musculoskeletal and connective tissue disorders																
Arthralgia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	2 (33. 33%)	1 (16. 67%)	1 (16.67 %)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	5 (8.06 %)	5 (3. 27%)

Back pain	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	3 (50. 00%)	2 (11. 11%)	1 (6.6 7%)	2 (6.9 0%)	9 (9.89 %)	1 (16. 67%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	3 (4.84 %)	12 (7 .84%)
Connec tive tissue disorde r	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Joint swellin g	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	2 (1. 31%)
Muscle spasms	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	1 (14. 29%)	2 (3.23 %)	3 (1. 96%)
Muscul ar weakne ss	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Muscul oskelet al chest pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	2 (1. 31%)
Muscul oskelet al pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	1 (14. 29%)	2 (3.23 %)	3 (1. 96%)
Myalgia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	2 (7.6 9%)	0 (0.00%)	0 (0.0 0%)	3 (4.84 %)	4 (2. 61%)
Neck pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	1 (14. 29%)	3 (4.84 %)	3 (1. 96%)
Osteop enia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Pain in extremi ty	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (14. 29%)	1 (1.61 %)	1 (0. 65%)
Tendon itis	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	2 (18.18 %)	0 (0.0 0%)	2 (3.23 %)	2 (1. 31%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)																
Tumour pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Nervous system disorders																
Ageusia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	3 (1. 96%)
Dizziness	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	1 (5.5 6%)	1 (6.6 7%)	0 (0.0 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (7.6 9%)	1 (9.09%)	0 (0.0 0%)	3 (4.84 %)	6 (3. 92%)
Dysgeusia	3 (50. 00%)	5 (41. 67%)	3 (60. 00%)	4 (66. 67%)	13 (7 2.22 %)	8 (53. 33%)	15 (5 1.72 %)	51 (56.0 4%)	1 (16. 67%)	2 (33. 33%)	3 (50.00 %)	12 (4 6.15 %)	5 (45.45 %)	1 (14. 29%)	24 (38.7 1%)	75 (4 9.02 %)
Headache	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	1 (5.5 6%)	0 (0.0 0%)	4 (13. 79%)	7 (7.69 %)	1 (16. 67%)	0 (0.0 0%)	1 (16.67 %)	1 (3.8 5%)	1 (9.09%)	1 (14. 29%)	5 (8.06 %)	12 (7 .84%)
Hyperaesthesia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Hypoaesthesia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Hypogeusia	0 (0.0 0%)	0 (0.0 0%)	2 (40. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	2 (1. 31%)
Neuralgia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	1 (16. 67%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	3 (1. 96%)

Neuropathy peripheral	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Paraesthesia	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Sciatica	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Somnolence	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Taste disorder	0 (0.0 0%)	2 (16. 67%)	0 (0.0 0%)	1 (16. 67%)	2 (11. 11%)	1 (6.6 7%)	3 (10. 34%)	9 (9.89 %)	1 (16. 67%)	1 (16. 67%)	0 (0.00%)	4 (15. 38%)	2 (18.18 %)	1 (14. 29%)	9 (14.52 %)	18 (1 1.76 %)
Psychiatric disorders																
Anxiety	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (6.9 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (7.6 9%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	5 (3. 27%)
Confusional state	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Depression	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Insomnia	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	1 (16. 67%)	0 (0.0 0%)	2 (13. 33%)	0 (0.0 0%)	4 (4.40 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	1 (9.09%)	0 (0.0 0%)	3 (4.84 %)	7 (4. 58%)
Mood altered	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	1 (9.09%)	0 (0.0 0%)	3 (4.84 %)	3 (1. 96%)
Sleep disorder	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Renal and urinary																

disorders																
Chromaturia	1 (16.67%)	3 (25.00%)	0 (0.0 0%)	4 (66.67%)	8 (44.44%)	7 (46.67%)	11 (37.93%)	34 (37.36%)	2 (33.33%)	2 (33.33%)	3 (50.00%)	14 (53.85%)	8 (72.73%)	1 (14.29%)	30 (48.39%)	64 (41.83%)
Dysuria	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61%)	1 (0.65%)
Haematuria	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61%)	1 (0.65%)
Pollakiuria	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.56%)	0 (0.0 0%)	1 (3.45%)	2 (2.20%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	0 (0.0 0%)	1 (1.61%)	3 (1.96%)
Renal colic	0 (0.0 0%)	1 (8.33%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (0.65%)
Renal failure	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.56%)	0 (0.0 0%)	1 (3.45%)	2 (2.20%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	2 (1.31%)
Urethral stenosis	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61%)	1 (0.65%)
Urinary incontinence	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.67%)	0 (0.0 0%)	1 (1.10%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (0.65%)
Urinary tract disorder	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.56%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.85%)	0 (0.00%)	0 (0.0 0%)	1 (1.61%)	2 (1.31%)
Reproductive system and breast disorders																
Benign prostatic	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61%)	1 (0.65%)

hyperplasia																
Breast pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Respiratory, thoracic and mediastinal disorders																
Cough	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (11. 11%)	0 (0.0 0%)	2 (6.9 0%)	4 (4.40 %)	1 (16. 67%)	0 (0.0 0%)	1 (16.67 %)	4 (15. 38%)	0 (0.00%)	0 (0.0 0%)	6 (9.68 %)	10 (6 .54%)
Dry throat	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Dyspnoea	0 (0.0 0%)	2 (16. 67%)	0 (0.0 0%)	4 (66. 67%)	2 (11. 11%)	3 (20. 00%)	1 (3.4 5%)	12 (13.1 9%)	0 (0.0 0%)	1 (16. 67%)	1 (16.67 %)	6 (23. 08%)	1 (9.09%)	0 (0.0 0%)	9 (14.52 %)	21 (1 3.73 %)
Dyspnoea exertional	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (3.4 5%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	1 (14. 29%)	2 (3.23 %)	4 (2. 61%)
Epistaxis	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	2 (13. 33%)	0 (0.0 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	3 (1. 96%)
Nasal congestion	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Oropharyngeal pain	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (7.6 9%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	2 (1. 31%)
Painful respiration	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)

Pulmonary embolism	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Rhinorrhoea	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Skin and subcutaneous tissue disorders																
Acne	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (33. 33%)	2 (11. 11%)	2 (13. 33%)	2 (6.9 0%)	8 (8.79 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	5 (19. 23%)	2 (18.18 %)	0 (0.0 0%)	8 (12.90 %)	16 (1 0.46 %)
Alopecia	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (7.6 9%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	2 (1. 31%)
Blister	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	2 (1. 31%)
Dermatitis acneiform	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	8 (27. 59%)	9 (9.89 %)	0 (0.0 0%)	1 (16. 67%)	1 (16.67 %)	2 (7.6 9%)	1 (9.09%)	0 (0.0 0%)	5 (8.06 %)	14 (9 .15%)
Dry skin	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	2 (6.9 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	4 (15. 38%)	0 (0.00%)	1 (14. 29%)	5 (8.06 %)	8 (5. 23%)
Eczema	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (7.6 9%)	0 (0.00%)	0 (0.0 0%)	2 (3.23 %)	4 (2. 61%)
Erythema	0 (0.0 0%)	1 (8.3 3%)	0 (0.0 0%)	1 (16. 67%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	3 (3.30 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	3 (1. 96%)
Hyperhidrosis	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	2 (13. 33%)	0 (0.0 0%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	2 (33.33 %)	1 (3.8 5%)	0 (0.00%)	1 (14. 29%)	4 (6.45 %)	6 (3. 92%)
Nail disorder	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	2 (1. 31%)

Night sweats	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	2 (33. 33%)	0 (0.0 0%)	1 (16.67 %)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	4 (6.45 %)	5 (3. 27%)
Photos ensitivit y reactio n	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Pruritus	1 (16. 67%)	1 (8.3 3%)	0 (0.0 0%)	1 (16. 67%)	3 (16. 67%)	1 (6.6 7%)	2 (6.9 0%)	9 (9.89 %)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67 %)	6 (23. 08%)	4 (36.36 %)	0 (0.0 0%)	11 (17.7 4%)	20 (1 3.07 %)
Rash	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	1 (6.6 7%)	7 (24. 14%)	9 (9.89 %)	3 (50. 00%)	0 (0.0 0%)	2 (33.33 %)	5 (19. 23%)	0 (0.00%)	0 (0.0 0%)	10 (16.1 3%)	19 (1 2.42 %)
Rash maculo - papular	0 (0.0 0%)	2 (16. 67%)	0 (0.0 0%)	0 (0.0 0%)	2 (11. 11%)	0 (0.0 0%)	1 (3.4 5%)	5 (5.49 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	3 (11. 54%)	0 (0.00%)	2 (28. 57%)	5 (8.06 %)	10 (6 .54%)
Skin burning sensati on	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (14. 29%)	1 (1.61 %)	1 (0. 65%)
Skin discolo uration	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	1 (16. 67%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Skin exfoliati on	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Skin hyperpi gmenta tion	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	1 (3.4 5%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (9.09%)	0 (0.0 0%)	1 (1.61 %)	3 (1. 96%)
Skin hypertr ophy	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (16. 67%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	1 (0. 65%)
Skin lesion	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)

Skin toxicity	0 (0.0 0%)	0 (0.0 0%)	1 (20. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)
Swellin g face	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (14. 29%)	1 (1.61 %)	2 (1. 31%)
Vascular disorder s																
Flushin g	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (5.5 6%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	1 (16. 67%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	2 (1. 31%)
Hot flush	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	1 (3.4 5%)	2 (2.20 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	0 (0.00%)	0 (0.0 0%)	1 (1.61 %)	3 (1. 96%)
Hyperte nsion	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (3.8 5%)	1 (9.09%)	1 (14. 29%)	3 (4.84 %)	3 (1. 96%)
Hypote nsion	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (6.6 7%)	0 (0.0 0%)	1 (1.10 %)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)	1 (0. 65%)

Other Relevant Findings

Conclusion:

The primary objective for the dose-escalation part of this study was to estimate the Maximum Tolerated Dose (MTD) and/or Recommended phase 2 dose (RDE) of sotrastaurin in patients with metastatic uveal melanoma. Two different dosing schedules (twice daily and three times daily) were explored in this study. The MTD for the twice daily dosing schedule was determined to be 700 mg twice daily (1400 mg total daily dose), and the RDE was 600 mg twice daily (1200 mg total daily dose) based on all of the safety and PK data available. For the three times daily dosing schedule, the MTD was determined to be 800 mg (total daily dose) or 300 mg/250 mg/250 mg, and 250 mg/250mg/250 mg (750 mg total daily dose) was selected as the RDE. Safety data remained consistent with the known safety profile of sotrastaurin. The most commonly reported AEs were GI related toxicities including nausea, constipation, vomiting, and diarrhea. Most grade 1 or grade 2 GI related AEs were manageable with co-medication or infrequently dose reduction/interruption and/or rarely resulted in premature discontinuation of the study drug. While AE incidence was similar for both dosing schedules, the twice daily dosing schedule was associated with more SAEs with suspected relationship to study drug according to the Investigator (13.2% vs. 9.7%), and more AEs leading to discontinuation (15.4% vs. 9.7%). This is likely due to the higher total daily dose (1400 mg for the MTD) compared with the RDE for the three times daily dosing schedule (250 mg three times daily for a total daily dose of 750 mg). Although limited RECIST responses were a factor in the enrollment halt for this study, of the 153 total patients in the FAS, four patients achieved a partial response, and 50% of patients had stable disease as

reported in the Primary CSR. No patients achieved a complete response. Median PFS for all patients was 3.5 months (80% CI, 2.6, 3.6) as reported in the Primary CSR. This modest evidence of potential clinical activity supports the idea that PKC inhibition in patients with metastatic uveal melanoma, a disease for which there are no currently approved therapies, warrants further exploration.

Date of Clinical Trial Report

13 Sep 2019