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Novartis Clinical Trial Results Template

Sponsor

Novartis

Generic Drug Name

LEQ506

Trial Indication(s)

Advanced solid tumors

Protocol Number

CLEQ506X2101

Protocol Title

A Phase I, multi-center, open label, dose escalation study of LEQ506, an oral smoothened inhibitor, in patients with advanced solid tumors.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

28-Oct-2010 (first patient first visit)/ 22-Jun-2015 (last patient last visit)

Reason for Termination (If applicable)

Main objectives of the trial had been achieved (24-Sep-2012: enrollment was permanently halted).

Study Design/Methodology

This was a Phase I, multi-center, open label dose escalation study of LEQ506, administered orally daily on a continuous 21-day dosing schedule, in adult patients with advanced solid tumors that had progressed despite standard treatments and for which no further standard therapies existed.

In the dose escalation phase, successive cohorts of patients were to receive increasing doses of LEQ506 until the maximum tolerated dose (MTD) was determined. Cohorts of at least 3 evaluable patients were treated at each dose level of LEQ506 from starting dose 80 mg once-a-day (qd) until MTD was reached.

After determination of the MTD, patients were enrolled in safety expansion phase at the MTD dose to further assess the safety and preliminary efficacy before the study enrollment was closed.

The pharmacokinetics (PK) run-in period, with administration of a single dose of LEQ506 on Day 1 followed by serial PK sampling over the subsequent 4 days (96 hours post-dose), was included in the dose escalation phase in order to characterize the single dose PK profile of LEQ506. There was no PK run-in period in the safety expansion phase.

Patients continued on the treatment with LEQ506 until disease progression or unacceptable toxicity occurred. Patients were discontinued from the study also if they withdrew consent, or if the investigator judged that further therapy would no longer in the patient's best interest. Final data for the study were analyzed when all patients continuing to receive treatment had completed at least three cycles or discontinued from the study.

Enrollment was permanently halted during the safety expansion phase. At this time, Novartis determined that the main objectives of the trial had been achieved, and that enrolling additional patients was not necessary and permanently halted enrollment of the study.

Centers

Netherlands (1 center) – Switzerland (1 center) – United Kingdom (1 center) – United States of America (2 centers).

Objectives:

Primary objective(s)

To determine the maximum tolerated dose (MTD) and characterize the dose limiting toxicities (DLT) of LEQ506 when administered orally on a continuous daily dosing schedule

Secondary objective(s)

- To characterize the safety and tolerability of LEQ506 treatment
- To characterize the pharmacokinetics of LEQ506 and any relevant metabolites
- To characterize the pharmacodynamic effects of LEQ506 by measuring Gli1 mRNA expression in normal skin and tumor samples (where available)
- To characterize any anti-tumor activity associated with LEQ506 treatment

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

LEQ506 capsules, 80-400 mg/day orally for a 21-day cycle; batch numbers: AEUS 2010-0069, AEUS 2010-0103, AEUS 2010-0070, AEUS 2012-0007, AEUS 2012-0006, and AEUS 2010-0068.

Statistical Methods

Efficacy analysis was based upon the full analysis set (FAS), which included all subjects who received at least one dose of LEQ506. A two-parameter Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle was used during the dose-escalation phase for dose level selection and for determination of the MTD. The MTD and DLT were based upon the dose-determining set (DDS), which consisted of all subjects from the safety set (at least within the dose-escalation part) who either met the required minimum exposure criterion and had sufficient safety evaluations, or discontinued earlier due to DLT (including during the PK run-in period). All other

safety tabulations were based on the safety set, which included those who received at least one dose of study drug and had at least one valid post-baseline safety assessment.

Study Population: Key Inclusion/Exclusion Criteria

Adult patients (aged ≥ 18 years) with a histologically or cytologically confirmed diagnosis of a solid tumor that had progressed despite standard therapy or for which no standard therapy existed, were enrolled onto the study. Patients with recurrent or refractory medulloblastoma (MB) were eligible for this study. Patients with basal cell carcinoma (BCC) who have advanced tumors that were no longer amenable to conventional treatment options, including surgery and radiotherapy, were also eligible for this study.

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Participant Flow Table

Patient disposition by treatment (Full Analysis Set)

	80 mg N=7 n (%)	120 mg N=5 n (%)	150 mg N=6 n (%)	200 mg N=12 n (%)	300 mg N=13 n (%)	400 mg N=14 n (%)	All patients N=57 n (%)
Treatment discontinued	7 (100)	5 (100)	6 (100)	12 (100)	13 (100)	14 (100)	57 (100)
Primary reason for end of treatment							
Adverse Event	0	1 (20.0)	2 (33.3)	1 (8.3)	2 (15.4)	5 (35.7)	11 (19.3)
Patient withdrew consent	0	0	1 (16.7)	1 (8.3)	0	3 (21.4)	5 (8.8)
Administrative problems[a]	0	0	0	0	2 (15.4)	0	2 (3.5)
Disease progression	7 (100)	4 (80.0)	3 (50.0)	10 (83.3)	9 (69.2)	6 (42.9)	39 (68.4)
Primary reason for study evaluation completion							
Patient withdrew consent	0	0	0	1 (8.3)	0	3 (21.4)	4 (7.0)
Lost to follow-up	0	0	1 (16.7)	0	1 (7.7)	0	2 (3.5)
Administrative problems[a]	0	0	0	0	2 (15.4)	0	2 (3.5)
Death	0	1 (20.0)	0	0	1 (7.7)	3 (21.4)	5 (8.8)
Disease progression	1 (14.3)	0	0	2 (16.7)	3 (23.1)	1 (7.1)	7 (12.3)
Follow-up phase completed as per protocol	6 (85.7)	4 (80.0)	5 (83.3)	9 (75.0)	6 (46.2)	7 (50.0)	37 (64.9)

a. In the 300 mg group, tumor of one patient shrunk during the study and the overall response was reported as partial response. The remaining of the lesion was assessed as "not a tumor" any more. Another patient had a SAE hyperbilirubinaemia (grade 2) and was hospitalized one day after commencing the study medication.
Study evaluation completion corresponds to the evaluation performed 28 days following treatment discontinuation
Data cutoff: 22-Jun-2015

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Baseline Characteristics

Demographic summary at baseline by treatment (full analysis set)

Demographic variables	80 mg N=7 n (%)	120 mg N=5 n (%)	150 mg N=6 n (%)	200 mg N=12 n (%)	300 mg N=13 n (%)	400 mg N=14 n (%)	All patients N=57 n (%)
Age (Years)							
n	7	5	6	12	13	14	57
Mean	54.1	57.0	58.2	51.5	56.8	61.2	56.6
SD	11.70	9.62	9.68	17.33	15.65	9.59	13.21
Median	49.0	56.0	59.5	49.0	60.0	61.5	59.0
Minimum	42.0	43.0	46.0	24.0	22.0	39.0	22.0
Maximum	74.0	67.0	70.0	78.0	78.0	77.0	78.0
Age category - n (%)							
< 65 years	6 (85.7)	3 (60.0)	4 (66.7)	9 (75.0)	9 (69.2)	9 (64.3)	40 (70.2)
≥ 65 years	1 (14.3)	2 (40.0)	2 (33.3)	3 (25.0)	4 (30.8)	5 (35.7)	17 (29.8)
Sex- n (%)							
Female	3 (42.9)	1 (20.0)	3 (50.0)	6 (50.0)	4 (30.8)	2 (14.3)	19 (33.3)
Male	4 (57.1)	4 (80.0)	3 (50.0)	6 (50.0)	9 (69.2)	12 (85.7)	38 (66.7)
Race - n (%)							
Asian	0	0	0	0	1 (7.7)	1 (7.1)	2 (3.5)
Caucasian	7 (100)	5 (100)	6 (100)	12 (100)	12 (92.3)	13 (92.9)	55 (96.5)
Ethnicity							
Chinese	0	0	0	0	1 (7.7)	0	1 (1.8)
Other	7 (100)	5 (100)	6 (100)	12 (100)	12 (92.3)	14 (100)	56 (98.2)
Weight (kg)							
n	7	5	5	12	13	14	56

Demographic variables	80 mg N=7 n (%)	120 mg N=5 n (%)	150 mg N=6 n (%)	200 mg N=12 n (%)	300 mg N=13 n (%)	400 mg N=14 n (%)	All patients N=57 n (%)
Mean	69.7	76.7	84.0	71.5	79.2	83.8	77.7
SD	11.13	17.05	21.10	15.98	13.16	20.67	16.94
Median	66.8	75.9	73.2	69.5	80.0	78.3	72.6
Minimum	57.4	57.2	62.3	52.8	58.0	56.2	52.8
Maximum	85.1	95.3	111.2	101.1	99.4	120.6	120.6
Height (cm)							
n	7	5	5	12	12	13	54
Mean	174.3	174.6	169.6	169.9	176.4	175.1	173.6
SD	14.13	11.65	12.97	11.66	8.48	7.35	10.39
Median	179.0	181.0	172.0	166.5	177.3	174.5	174.5
Minimum	160.0	160.0	149.0	155.3	163.0	165.0	149.0
Maximum	192.0	184.0	185.0	190.0	193.0	188.0	193.0
Body surface area (m2)							
n	7	5	5	12	12	13	54
Mean	1.8	1.9	2.0	1.8	2.0	2.0	1.9
SD	0.20	0.27	0.30	0.25	0.20	0.29	0.25
Median	1.8	2.0	1.9	1.8	2.0	2.0	1.9
Minimum	1.6	1.6	1.7	1.5	1.7	1.6	1.5
Maximum	2.1	2.2	2.4	2.3	2.3	2.5	2.5
Body mass index (kg/m2)							
n	7	5	5	12	12	13	54
Mean	23.0	24.9	29.1	24.6	25.4	26.8	25.5
SD	2.96	3.01	5.66	3.70	3.61	5.78	4.46
Median	23.7	23.3	32.4	23.9	25.3	25.7	24.7

Demographic variables	80 mg N=7 n (%)	120 mg N=5 n (%)	150 mg N=6 n (%)	200 mg N=12 n (%)	300 mg N=13 n (%)	400 mg N=14 n (%)	All patients N=57 n (%)
Minimum	18.8	22.3	21.1	19.9	18.0	19.6	18.0
Maximum	26.6	28.1	34.3	32.3	30.5	36.8	36.8
WHO performance status- n (%)							
0	3 (42.9)	2 (40.0)	2 (33.3)	3 (25.0)	4 (30.8)	2 (14.3)	16 (28.1)
1	3 (42.9)	3 (60.0)	4 (66.7)	9 (75.0)	8 (61.5)	12 (85.7)	39 (68.4)
Missing	1 (14.3)	0	0	0	1 (7.7)	0	2 (3.5)

SD = Standard deviation
Body Mass Index: BMI [kg/m2] = weight[kg] / (height[m]2)
Body Surface Area (Gehan and George): BSA[m2]=234.94(height[cm]0.422)*(weight[kg]0.515)/10000

Summary of Efficacy

Primary Outcome Result(s)

Summary of posterior distribution of DLT rates at the end of study (Dose Determining set)

Dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval					Quantile		
	0 – 0.16	0.16 – 0.33	0.33 – 1	Mean	SD	2.5%	50%	97.5%
80	1	0	0	0.01	0.013	0	0.006	0.048
120	1	0	0	0.02	0.018	0.001	0.015	0.068
150	1	0	0	0.03	0.022	0.003	0.024	0.087
200	0.994	0.006	0	0.05	0.031	0.009	0.044	0.127
300	0.839	0.16	0.001	0.11	0.052	0.031	0.102	0.229
400	0.395	0.559	0.047	0.19	0.078	0.054	0.18	0.358

DLTs occurring during the first cycle by primary system organ class, preferred term, and treatment (Dose determining set)

Primary system organ class Preferred term	200 mg N=10 n (%)	400 mg N=12 n (%)	All subjects N=49 n (%)
Any primary system organ class	1 (10.0)	3 (25.0)	4 (8.2)
General Disorders and Administration Site Conditions	0	2 (16.7)	2 (4.1)
Fatigue	0	2 (16.7)	2(4.1)
Investigations	1 (10.0)	1 (8.3)	2 (4.1)
Alanine Aminotransferase Increased	0	1 (8.3)	1 (2.0)
Aspartate Aminotransferase Increased	0	1 (8.3)	1 (2.0)
Blood Creatine Phosphokinase Increased	1 (10.0)	0	1 (2.0)
Blood Uric Acid Increased	0	1 (8.3)	1 (2.0)
Respiratory, Thoracic And Mediastinal Disorders	0	1 (8.3)	1 (2.0)
Dyspnoea	0	1 (8.3)	1 (2.0)

Secondary Outcome Result(s)

Summary statistics of Gli1 expression from paraffin-embedded tissue and fold change from baseline – Full analysis set

Timepoint		80 mg QD N=7	120 mg QD N=5	150 mg QD N=6	200 mg QD N=12	300 mg QD N=13	400 mg QD N=14	All patients N=57
Screening	n (%)	6 (85.7)	4 (80.0)	3 (50.0)	4 (33.3)	6 (46.2)	9 (64.3)	32 (56.1)
	Mean (SD)	-7.1 (1.26)	-7.5 (0.79)	-6.2 (0.56)	-6.0 (1.10)	-5.9 (1.20)	-5.7 (1.02)	-6.3 (1.19)
	Median	-7.4	-7.4	-6.2	-5.7	-5.7	-5.5	-6.3
	Min; Max	-8.3; -4.6	-8.5; -6.6	-6.7; -5.6	-7.6; -5.1	-7.6; -4.4	-7.4; -4.2	-8.5; -4.2
Cycle 1 Day 21	n (%)	6 (85.7)	4 (80.0)	3 (50.0)	3 (25.0)	6 (46.2)	8 (57.1)	30 (52.6)
	Mean (SD)	-8.8 (2.38)	-10.0 (1.19)	-7.9 (1.23)	-8.0 (1.27)	-7.9 (0.86)	-9.4 (0.60)	-8.8 (1.46)
	Median	-9.6	-10.1	-7.8	-8.1	-8.0	-9.2	-9.0
	Min; Max	-11.6; -4.7	-11.2; -8.5	-9.2; -6.8	-9.3; -6.7	-9.0; -6.7	-10.5; -8.6	-11.6; -4.7
Fold change from screening	n (%)	6 (85.7)	4 (80.0)	3 (50.0)	3 (25.0)	5 (38.5)	8 (57.1)	29 (50.9)
	Mean	-4.5	-6.1	-4.6	-8.5	-7.0	-15.2	-8.5
	Median	-4.5	-5.5	-4.6	-4.9	-6.2	-12.7	-6.2
	Min; Max	-9.8; -1.1	-9.7; -3.7	-8.1; -1.1	-18.4; -2.3	-13.5; -1.4	-29.0; -3.0	-29.0; -1.1
End of treatment	n (%)	3 (42.9)	0	1 (16.7)	2 (16.7)	3 (23.1)	3 (21.4)	12 (21.1)
	Mean (SD)	-6.8 (2.20)	0	-8.4 (0)	-6.5 (2.05)	-5.9 (1.00)	-6.5 (3.27)	-6.6 (1.96)
	Median	-7.8	0	-8.4	-6.5	-5.4	-5.8	-6.4
	Min; Max	-8.4; -4.3	0	-8.4; -8.4	-8.0; -5.1	-7.0; -5.2	-10.0; -3.6	-10.0; -3.6
Fold change from screening	n (%)	3 (42.9)	0	1 (16.7)	2 (16.7)	2 (15.4)	3 (21.4)	11 (19.3)
	Mean	1.5	0	-4.5	0	1.4	-0.6	0.1
	Median	-1.3	0	-4.5	0	1.4	1.1	1.1

Timepoint		80 mg QD N=7	120 mg QD N=5	150 mg QD N=6	200 mg QD N=12	300 mg QD N=13	400 mg QD N=14	All patients N=57
	Min; Max	-2.2; 8.1	0	-4.5; -4.5	-1.3; 1.4	1.2; 1.5	-6.2; 3.4	-6.2; 8.1

When baseline or post baseline value is below the lower limit of quantification, fold-change from baseline is not imputed and reported as missing.
Data cutoff: 22-Jun-2015

Summary of pharmacokinetic parameters of LEQ506 by treatment (PK set)

Parameter (PK Run in)	Statistics	80 mg N=7	120 mg N=5	150 mg N=6	200 mg N=11	300 mg N=13	400 mg N=11
AUC0-168h (hr*ng/mL)	n	6	5	6	11	13	7
	Mean (SD)	11100 (9190)	13700 (7590)	20300 (15300)	21900 (8500)	41000 (38200)	49800 (24800)
AUC0-24h (hr*ng/mL)	n	6	5	6	11	13	7
	Mean (SD)	6900(4700)	6150 (3960)	6950 (2550)	14400 (8120)	20400(14900)	26200 (16600)
AUCinf (ng*hr/mL)	n	6	5	5	11	11	6
	Mean (SD)	11100 (9320)	14300 (7970)	23700 (18800)	21800 (8520)	34200(22300)	54000 (25800)
CL/F (mL/hr)	n	6	5	5	11	11	6
	Mean (SD)	9920 (4420)	15500 (18200)	11500 (9030)	11000 (6140)	12800 (9730)	9070 (4290)
Cmax (ng/mL)	n	7	5	6	11	13	7
	Mean (SD)	832 (514)	409 (296)	523 (285)	1510 (1030)	2100 (1600)	2080 (1380)
Tmax (hr)	n	7	5	6	11	13	7
	Median	2.00	4.00	4.00	2.20	2.00	3.98
	[Min; Max]	[0.500; 6.00]	[0.500; 6.00]	[1.00; 25.9]	[0.500; 6.17]	[0.667; 24.0]	[0.533; 24.0]
V/F (mL)	n	6	5	5	11	11	6
	Mean (SD)	201000 (84800)	398000 (210000)	345000 (250000)	250000 (226000)	363000 (370000)	295000 (129000)
T1/2 (hr)	n	6	5	5	11	12	6
	Median	15.7	20.7	22.6	13.7	17.3	22.3
	[Min; Max]	[7.98; 21.1]	[9.08; 65.7]	[11.3; 58.2]	[8.75; 22.1]	[9.17; 46.1]	[10.2; 41.6]
Lambda_z (1/hr)	n	6	5	5	11	12	6
	Mean (SD)	0.0512 (0.0207)	0.0360 (0.0247)	0.0344 (0.0200)	0.0536 (0.0178)	0.0411 (0.0192)	0.0345 (0.0188)

Parameter (C1D15)	Statistics	80 mg N=7	120 mg N=5	150 mg N=6	200 mg N=11	300 mg N=13	400 mg N=11
AUC0-24h (hr*ng/mL)	n	6	5	5	8	11	3
	Mean (SD)	7430(3920)	18000 (11900)	21900 (14100)	24400 (13500)	29400 (17400)	25200 (11600)
Cmax (ng/mL)	n	7	5	5	9	12	4
	Mean (SD)	869 (686)	1290 (762)	1510 (889)	2130 (1360)	2490 (1380)	2570 (1570)
Cmin,ss (ng/mL)	n	7	5	5	10	12	4
	Mean (SD)	302 (309)	548 (353)	842 (502)	678 (414)	797 (645)	1670 (1270)
Racc (fold)	n	5	5	5	8	11	3
	Median	1.62	2.91	2.52	1.60	1.96	1.36
	[Min; Max]	[0.186; 2.43]	[1.27; 3.56]	[1.15; 6.74]	[0.680; 6.12]	[0.874; 4.67]	[1.10; 1.88]
Tmax (hr)	n	7	5	5	9	12	4
	Median	2.00	1.08	4.00	2.00	2.00	2.63
	[Min; Max]	[0; 6.00]	[1.00; 6.00]	[1.00; 4.03]	[0.500; 5.58]	[0.667; 8.00]	[1.00; 6.02]

Tmax, accumulation ratio and T1/2 values are displayed as n, median, and range; Cmin, ss is the predose concentration on C1D15
Racc is calculated by AUC0-24h on C1D15 divided by AUC0-24h on PK run-in.

Summary of best overall response by treatment (Full analysis set)

	80 mg N=7 n (%)	120 mg N=5 n (%)	150 mg N=6 n (%)	200 mg N=12 n (%)	300 mg N=13 n (%)	400 mg N=14 n (%)	All Subjects N=57 n (%)
Best overall response							
Partial response (PR)	1 (14.3)	1 (20.0)	1 (16.7)	2 (16.7)	1 (7.7)	0	6 (10.5)
Stable disease (SD)	2 (28.6)	1 (20.0)	0	5 (41.7)	3 (23.1)	4 (28.6)	15 (26.3)
Progressive disease (PD)	4 (57.1)	3 (60.0)	3 (50.0)	4 (33.3)	6 (46.2)	4 (28.6)	24 (42.1)
Unknown	0	0	2 (33.3)	1 (8.3)	3 (23.1)	5 (35.7)	11 (19.3)
Not assessed	0	0	0	0	0	1 (7.1)	1 (1.8)

PD = progressive disease PR = partial response, SD= stable disease
Best overall response was to be based on investigator's assessment of disease status using RECIST v1.0 for patients with solid tumors or Neuro-oncology criteria for medulloblastoma. There were 3 patients with medulloblastoma who were evaluated using RECIST.

Summary of Safety

Safety Results

Frequent adverse events (at least 10%*) by primary system organ class - Safety set

	80 mg N=7 n (%)	120 mg N=5 n (%)	150 mg N=6 n (%)	200 mg N=12 n (%)	300 mg N=13 n (%)	400 mg N=14 n (%)	All patients N=57 n (%)
Any primary system organ class	7 (100)	5 (100)	6 (100)	12 (100)	13 (100)	14 (100)	57 (100)
Gastrointestinal disorders	5 (71.4)	3 (60.0)	6 (100)	11 (91.7)	9 (69.2)	10 (71.4)	44 (77.2)
Musculoskeletal and connective tissue disorders	4 (57.1)	4 (80.0)	4 (66.7)	10 (83.3)	10 (76.9)	9 (64.3)	41 (71.9)
General disorders and administration site conditions	6 (85.7)	5 (100)	5 (83.3)	8 (66.7)	7 (53.8)	9 (64.3)	40 (70.2)
Metabolism and nutrition disorders	3 (42.9)	2 (40.0)	6 (100)	9 (75.0)	8 (61.5)	7 (50.0)	35 (61.4)
Nervous system disorders	3 (42.9)	2 (40.0)	4 (66.7)	8 (66.7)	8 (61.5)	9 (64.3)	34 (59.6)
Investigations	4 (57.1)	2 (40.0)	3 (50.0)	5 (41.7)	5 (38.5)	6 (42.9)	25 (43.9)
Respiratory, thoracic and mediastinal disorders	3 (42.9)	2 (40.0)	3 (50.0)	5 (41.7)	5 (38.5)	5 (35.7)	23 (40.4)
Skin and subcutaneous tissue disorders	4 (57.1)	1 (20.0)	1 (16.7)	7 (58.3)	7 (53.8)	2 (14.3)	22 (38.6)
Blood and lymphatic system disorders	4 (57.1)	0	0	3 (25.0)	2 (15.4)	5 (35.7)	14 (24.6)
Infections and infestations	2 (28.6)	0	2 (33.3)	6 (50.0)	2 (15.4)	2 (14.3)	14 (24.6)
Psychiatric disorders	1 (14.3)	1 (20.0)	1 (16.7)	2 (16.7)	2 (15.4)	2 (14.3)	9 (15.8)
Vascular disorders	2 (28.6)	1 (20.0)	1 (16.7)	3 (25.0)	0	1 (7.1)	8 (14.0)
Renal and urinary disorders	1 (14.3)	0	0	1 (8.3)	2 (15.4)	3 (21.4)	7 (12.3)

	80 mg N=7 n (%)	120 mg N=5 n (%)	150 mg N=6 n (%)	200 mg N=12 n (%)	300 mg N=13 n (%)	400 mg N=14 n (%)	All patients N=57 n (%)
Eye disorders	2 (28.6)	0	0	1 (8.3)	2 (15.4)	1 (7.1)	6 (10.5)

* 10% is based on “all patients” column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple AEs is counted only once in the total row. Only AEs occurring during treatment or within 28 days of the last study medication are reported. Primary system organ classes are presented in descending frequency as reported in the “All patients” column.
Data cutoff: 22-Jun-2015

Frequent (at least 10%*) adverse events by preferred term and grade3/4 - Safety set

	80 mg N=7		120 mg N=5		150 mg N=6		200 mg N=12		300 mg N=13		400 mg N=14		All patients N=57	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Any preferred term	7 (100)	6 (85.7)	5 (100)	2 (40.0)	6 (100)	3 (50.0)	12 (100)	8 (66.7)	13 (100)	5 (38.5)	14 (100)	9 (64.3)	57 (100)	33 (57.9)
Fatigue	5 (71.4)	0	4 (80.0)	1 (20.0)	5 (83.3)	1 (16.7)	7 (58.3)	0	7 (53.8)	0	9 (64.3)	4 (28.6)	37 (64.9)	6 (10.5)
Nausea	5 (71.4)	0	3 (60.0)	0	4 (66.7)	0	10 (83.3)	0	5 (38.5)	0	7 (50.0)	0	34 (59.6)	0
Decreased appetite	2 (28.6)	0	2 (40.0)	0	5 (83.3)	0	9 (75.0)	0	6 (46.2)	0	6 (42.9)	0	30 (52.6)	0
Vomiting	4 (57.1)	1 (14.3)	2 (40.0)	0	3 (50.0)	0	4 (33.3)	0	4 (30.8)	0	4 (28.6)	0	21 (36.8)	1 (1.8)
Muscle spasms	1 (14.3)	0	1 (20.0)	0	1 (16.7)	0	5 (41.7)	0	5 (38.5)	0	7 (50.0)	0	20 (35.1)	0
Dysgeusia	2 (28.6)	0	1 (20.0)	0	4 (66.7)	0	4 (33.3)	0	2 (15.4)	0	6 (42.9)	0	19 (33.3)	0
Constipation	4 (57.1)	0	1 (20.0)	0	1 (16.7)	0	7 (58.3)	1 (8.3)	0	0	3 (21.4)	0	16 (28.1)	1 (1.8)
Back Pain	2 (28.6)	0	0	0	1 (16.7)	1 (16.7)	5 (41.7)	1 (8.3)	4 (30.8)	0	0	0	12 (21.1)	2 (3.5)
Diarrhoea	1 (14.3)	0	1 (20.0)	0	2 (33.3)	0	5 (41.7)	0	1 (7.7)	0	2 (14.3)	1 (7.1)	12 (21.1)	1 (1.8)
Abdominal pain	0	0	1 (20.0)	0	1 (16.7)	0	2 (16.7)	2 (16.7)	3 (23.1)	0	4 (28.6)	1 (7.1)	11 (19.3)	3 (5.3)

	80 mg N=7		120 mg N=5		150 mg N=6		200 mg N=12		300 mg N=13		400 mg N=14		All patients N=57	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Alopecia	1 (14.3)	0	1 (20.0)	0	1 (16.7)	0	5 (41.7)	0	3 (23.1)	0	0	0	11 (19.3)	0
Cough	1 (14.3)	0	2 (40.0)	0	1 (16.7)	0	2 (16.7)	0	3 (23.1)	0	2 (14.3)	0	11 (19.3)	0
Dyspnoea	1 (14.3)	0	0	0	2 (33.3)	0	2 (16.7)	0	4 (30.8)	1 (7.7)	2 (14.3)	1 (7.1)	11 (19.3)	2 (3.5)
Myalgia	1 (14.3)	0	1 (20.0)	0	2 (33.3)	0	3 (25.0)	2 (16.7)	2 (15.4)	0	2 (14.3)	0	11 (19.3)	2 (3.5)
Anaemia	3 (42.9)	0	0	0	0	0	2 (16.7)	0	2 (15.4)	0	3 (21.4)	0	10 (17.5)	0
Pyrexia	2 (28.6)	0	2 (40.0)	0	1 (16.7)	0	1 (8.3)	0	0	0	3 (21.4)	0	9 (15.8)	0
Arthralgia	1 (14.3)	0	1 (20.0)	0	1 (16.7)	0	4 (33.3)	0	0	0	1 (7.1)	0	8 (14.0)	0
Dizziness	1 (14.3)	0	1 (20.0)	0	1 (16.7)	0	3 (25.0)	0	1 (7.7)	0	1 (7.1)	0	8 (14.0)	0
Weight decreased	1 (14.3)	0	0	0	2 (33.3)	1 (16.7)	3 (25.0)	0	2 (15.4)	1 (7.7)	0	0	8 (14.0)	2 (3.5)
Blood alkaline phosphatase increased	1 (14.3)	1 (14.3)	0	0	1 (16.7)	0	2 (16.7)	1 (8.3)	1 (7.7)	1 (7.7)	2 (14.3)	1 (7.1)	7 (12.3)	4 (7.0)
Alanine aminotransferase increased	1 (14.3)	0	1 (20.0)	1 (20.0)	0	0	2 (16.7)	0	0	0	2 (14.3)	1 (7.1)	6 (10.5)	2 (3.5)
Dyspepsia	1 (14.3)	0	0	0	1 (16.7)	0	2 (16.7)	0	1 (7.7)	0	1 (7.1)	0	6 (10.5)	0

* 10% is based on “all patients” column.
Preferred terms are presented in descending frequency as reported in the “All patients” column. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple AEs within a preferred term is counted only once in the total row. Only AEs occurring during treatment or within 28 days of the last study medication are reported.
Data cutoff: 22-Jun-2015

Details of patients who died

Treatment group	Age/Sex/Race	Study day of last dose	Study day of death	Principal Cause of Death
120 mg				
	67/M/Ca	42	51	Progression of pancreas carcinoma

Treatment group	Age/Sex/Race	Study day of last dose	Study day of death	Principal Cause of Death
300 mg				
	55/M/Ca	42	66	Gastric cancer
400 mg				
	59/M/As	22	48	Progressive rectum carcinoma
	77/M/Ca	21	31	Metastatic colorectal cancer
	48/M/Ca	84	85	Related to disease[a]

As = Asian, Ca= Caucasian, M= male
Study day is relative to the first day of treatment (day 1).
Patients who died within 28 day after last dose of study drug or other deaths reported on end of treatment page.
a The patient was diagnosed with an intracranial hemorrhage, likely due to anticoagulant concomitant; however, the patient's principal cause of death was reported as "related to disease".

Summary of SAEs, regardless of relationship to study drug, by preferred term and treatment-Safety set

Preferred term	80 mg N=7 n (%)	120 mg N=5 n (%)	150 mg N=6 n (%)	200 mg N=12 n (%)	300 mg N=13 n (%)	400 mg N=14 n (%)	All Subjects N=57 n (%)
Total	4 (57.1)	3 (60.0)	2 (33.3)	2 (16.7)	3 (23.1)	6 (42.9)	20 (35.1)
Abdominal Pain	0	0	0	1 (8.3)	0	1 (7.1)	2 (3.5)
Cholangitis	0	1 (20.0)	0	0	0	1 (7.1)	2 (3.5)
Dyspnoea	1 (14.3)	0	1 (16.7)	0	0	0	2 (3.5)
Fatigue	0	0	0	0	0	2 (14.3)	2 (3.5)
Pyrexia	1 (14.3)	0	1 (16.7)	0	0	0	2 (3.5)
Abdominal Abscess	1 (14.3)	0	0	0	0	0	1 (1.8)
Abdominal Distension	1 (14.3)	0	0	0	0	0	1 (1.8)
Abscess	1 (14.3)	0	0	0	0	0	1 (1.8)
Alanine Aminotransferase Increased	0	1 (20.0)	0	0	0	0	1 (1.8)
Ascites	0	0	0	0	0	1 (7.1)	1 (1.8)

Preferred term	80 mg N=7 n (%)	120 mg N=5 n (%)	150 mg N=6 n (%)	200 mg N=12 n (%)	300 mg N=13 n (%)	400 mg N=14 n (%)	All Subjects N=57 n (%)
Aspartate Aminotransferase Increased	0	1 (20.0)	0	0	0	0	1 (1.8)
Atrial Fibrillation	1 (14.3)	0	0	0	0	0	1 (1.8)
Back Pain	0	0	1 (16.7)	0	0	0	1 (1.8)
Blood Bilirubin Increased	0	1 (20.0)	0	0	0	0	1 (1.8)
Constipation	0	0	0	1 (8.3)	0	0	1 (1.8)
Deep Vein Thrombosis	0	0	0	1 (8.3)	0	0	1 (1.8)
Duodenal Obstruction	0	0	0	0	0	1 (7.1)	1 (1.8)
Electrocardiogram QT Prolonged	0	0	0	0	0	1 (7.1)	1 (1.8)
Haemorrhage Intracranial	0	0	0	0	0	1 (7.1)	1 (1.8)
Hyperbilirubinaemia	0	0	0	0	1 (7.7)	0	1 (1.8)
Implant Site Abscess	0	0	0	0	1 (7.7)	0	1 (1.8)
Intestinal Obstruction	1 (14.3)	0	0	0	0	0	1 (1.8)
Oedema Peripheral	0	0	0	0	0	1 (7.1)	1 (1.8)
Overdose	0	1 (20.0)	0	0	0	0	1 (1.8)
Pleural Effusion	0	0	0	0	1 (7.7)	0	1 (1.8)
Vomiting	1 (14.3)	0	0	0	0	0	1 (1.8)
Wound Infection	1 (14.3)	0	0	0	0	0	1 (1.8)

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

Patients who experienced AEs leading to discontinuation of study treatment-Safety set

Preferred Term	Treatment	Worst Grade
Fatigue	120 mg	1
	150 mg	2

Preferred Term	Treatment	Worst Grade
	300 mg	2
	400 mg	3
Nausea	120 mg	1
	150 mg	2
Vomiting	120 mg	1
	150 mg	2
Dysgeusia	150 mg	2
	400 mg	2
Muscle spasms	400 mg	1
	400 mg	2
Abdominal pain	200 mg	3
Implant site abscess	300 mg	3
Decreased appetite	400 mg	2
Dyspnoea	400 mg	3
Haemorrhage intracranial	400 mg	4
Electrocardiogram QT prolonged	400 mg	3

Other Relevant Findings

CTC Grade 3/4 new or worsened hematology abnormalities based on CTC grade by treatment-Safety set

		80 mg (N=7)			120 mg (N=5)			150 mg (N=6)			200 mg (N=12)			300 mg (N=13)			400 mg (N=14)			All patients (N=57)		
Test	**Worsening from baseline to**	**Total**	**n**	**%**	**Total**	**n**	**%**	**Total**	**n**	**%**	**Total**	**n**	**%**	**Total**	**n**	**%**	**Total**	**n**	**%**	**Total**	**n**	**%**
Absolute Lymphocytes (hypo)	Grade 3	7	0	0.0	5	0	0.0	6	1	16.7	11	2	18.2	11	2	18.2	14	0	0.0	54	5	9.3
-	Grade 4	7	0	0.0	5	0	0.0	6	0	0.0	12	1	8.3	13	0	0.0	14	0	0.0	57	1	1.8
Absolute Neutrophils (hypo)	Grade 3	7	0	0.0	5	0	0.0	6	1	16.7	12	0	0.0	13	0	0.0	14	0	0.0	57	1	1.8
Hemoglobin (hypo)	Grade 3	7	0	0.0	5	0	0.0	6	0	0.0	12	1	8.3	13	0	0.0	14	0	0.0	57	1	1.8

Test	Worsening from baseline to	80 mg (N=7)			120 mg (N=5)			150 mg (N=6)			200 mg (N=12)			300 mg (N=13)			400 mg (N=14)			All patients (N=57)		
		Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%
WBC (hypo)	Grade 3	7	0	0.0	5	0	0.0	6	1	16.7	12	1	8.3	13	0	0.0	14	0	0.0	57	2	3.5
Prothrombin Time INR (hyper)	Grade 3	4	0	0.0	3	0	0.0	2	0	0.0	9	0	0.0	6	1	16.7	6	0	0.0	30	1	3.3
Fibrinogen (hypo)	Grade 3	7	1	14.3	3	0	0.0	4	0	0.0	11	0	0.0	9	0	0.0	11	0	0.0	45	1	2.2

Total = number of patients evaluable post-baseline, who had less than grade x at baseline.
n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
Patients are counted only for the worst grade observed post-baseline.
Baseline is defined as the last non-missing value prior to the first dose.

CTC Grade 3/4 new or worsened clinical chemistry abnormalities based on CTC grade by treatment-Safety set

Test	Worsening from baseline to	80 mg (N=7)			120 mg (N=5)			150 mg (N=6)			200 mg (N=12)			300 mg (N=13)			400 mg (N=14)			All patients (N=57)		
		Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%
Alkaline phosphatase, serum (hyper)	Grade-3	7	1	14.3	4	0	0.0	5	0	0.0	12	2	16.7	13	1	7.7	14	1	7.1	55	5	9.1
Creatinine (Hyper)	Grade-3	7	0	0.0	5	0	0.0	6	0	0.0	12	0	0.0	13	0	0.0	14	1	7.1	57	1	1.8
Potassium (hypo)	Grade-3	7	1	14.3	5	0	0.0	6	0	0.0	11	0	0.0	13	1	7.7	14	1	7.1	56	3	5.4
Potassium (hyper)	Grade-3	7	0	0.0	5	0	0.0	6	0	0.0	11	0	0.0	13	1	7.7	14	1	7.1	56	2	3.6
SGOT (AST) (hyper)	Grade-3	7	1	14.3	5	1	20.0	6	0	0.0	11	0	0.0	13	0	0.0	14	1	7.1	56	3	5.4
SGPT (ALT) (hyper)	Grade-3	7	0	0.0	5	1	20.0	6	0	0.0	12	0	0.0	13	0	0.0	14	1	7.1	57	2	3.5
Sodium (hypo)	Grade-3	7	0	0.0	5	1	20.0	6	0	0.0	10	1	10.0	13	0	0.0	14	1	7.1	55	3	5.5
Total Bilirubin (hyper)	Grade-3	7	0	0.0	5	1	20.0	6	0	0.0	12	1	8.3	13	0	0.0	14	0	0.0	57	2	3.5
Total Cholesterol (hyper)	Grade-3	6	0	0.0	5	0	0.0	6	1	16.7	11	0	0.0	13	0	0.0	14	0	0.0	55	1	1.8
Phosphate (hypo)	Grade-3	6	0	0.0	5	0	0.0	6	1	16.7	11	0	0.0	12	2	16.7	14	0	0.0	54	3	5.6

Total = number of subjects evaluable post-baseline, who had less than grade x at baseline.
n = number of subjects who had missing or less than grade x at baseline, and worsened to grade x post-baseline.

Test	Worsening from baseline to	80 mg (N=7) Total n	%	120 mg (N=5) Total n	%	150 mg (N=6) Total n	%	200 mg (N=12) Total n	%	300 mg (N=13) Total n	%	400 mg (N=14) Total n	%	All patients (N=57) Total n	%
Subjects are counted only for the worst grade observed post-baseline. Baseline is defined as the last non-missing value prior to the first dose.															

Notably abnormal vital sign and weight values by treatment (Safety set)

Weight and Vital sign	Category	80 mg N=7 N (%)	120 mg N=5 N (%)	150 mg N=6 N (%)	200 mg N=12 N (%)	300 mg N=13 N (%)	400 mg N=14 N (%)	All Subjects N=57 N (%)
Weight (kg)	N*	7	5	5	12	13	13	55
	Low only	0	0	0	0	1 (7.7)	2 (15.4)	3 (5.5)
Sitting Pulse (bpm)	N*	7	5	6	12	13	14	57
	High only	0	0	0	1 (8.3)	0	2 (14.3)	3 (5.3)
	Low only	0	1 (20.0)	1 (16.7)	0	0	0	2 (3.5)
Sitting Systolic Blood Pressure (mmHg)	N*	7	5	6	12	13	14	57
	Low only	1 (14.3)	0	0	0	0	1 (7.1)	2 (3.5)
Sitting Diastolic Blood Pressure (mmHg)	N*	7	5	6	12	13	14	57
	Low only	0	0	0	1 (8.3)	0	0	1 (1.8)
Body Temperature (°C)	N*	7	5	6	12	13	14	57
	High only	2 (28.6)	2 (40.0)	3 (50.0)	1 (8.3)	1 (7.7)	3 (21.4)	12 (21.1)
	Low only	0	0	0	0	1 (7.7)	0	1 (1.8)

Notably abnormal vital signs:
Weight [kg]: increase/decrease from baseline of ≥20%
Body temperature [ºC]: ≥37.5ºC/≤35 ºC
Systolic blood pressure [mmHg]: ≥180 mmHg/≤90 mmHg with increase/decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]: ≥105 mmHg/≤50 mmHg with increase/decrease from baseline of ≥15 mmHg
Pulse rate [bpm]: ≥120 bpm/≤50 bpm with increase/decrease from baseline of ≥15 bpm
*N is the total number of subjects with baseline and post baseline values, which is used to calculate the percentage.

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Notably abnormal ECG values by treatment- Safety set

	80 mg (N=7)			120 mg (N=5)			150 mg (N=6)			200 mg (N=12)			300 mg (N=13)			400 mg (N=14)			All patients (N=57)		
	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%
QTcF (msec)																					
New >450	7	0	0	5	0	0	6	2	33.3	12	0	0	13	3	23.1	14	2	14.3	57	7	12.3
New >480	7	0	0	5	0	0	6	0	0	12	0	0	13	0	0	14	1	7.1	57	1	1.8
New >500	7	0	0	5	0	0	6	0	0	12	0	0	13	0	0	14	1	7.1	57	1	1.8
Increase from baseline >30	7	0	0	5	1	20.0	6	2	33.3	12	2	16.7	13	1	7.7	14	3	21.4	57	9	15.8
Increase from baseline >60	7	0	0	5	0	0	6	0	0	12	0	0	13	0	0	14	1	7.1	57	1	1.8
QTcB (msec)																					
New >450	6	1	16.7	4	1	25.0	5	3	60.0	12	2	16.7	12	3	25.0	13	5	38.5	52	15	28.8
New >480	7	0	0	5	0	0	6	1	16.7	12	0	0	13	0	0	14	2	14.3	57	3	5.3
New >500	7	0	0	5	0	0	6	1	16.7	12	0	0	13	0	0	14	1	7.1	57	2	3.5
Increase from baseline >30	7	1	14.3	5	0	0	6	5	83.3	12	2	16.7	13	3	23.1	14	5	35.7	57	16	28.1
Increase from baseline >60	7	0	0	5	0	0	6	0	0	12	0	0	13	0	0	14	0	0	57	0	0
QT (msec)																					
New >450	7	0	0	5	1	20.0	6	2	33.3	12	1	8.3	11	3	27.3	14	2	14.3	55	9	16.4
New >480	7	0	0	5	0	0	6	1	16.7	12	0	0	13	2	15.4	14	1	7.1	57	4	7.0
New >500	7	0	0	5	0	0	6	0	0	12	0	0	13	1	7.7	14	0	0	57	1	1.8
Increase from baseline >30	7	2	28.6	5	4	80.0	6	3	50.0	12	4	33.3	13	4	30.8	14	2	14.3	57	19	33.3
Increase from baseline >60	7	0	0	5	0	0	6	1	16.7	12	1	8.3	13	1	7.7	14	1	7.1	57	4	7.0
HR (bpm)																					
RR decrease >25% & to a HR>100	7	1	14.3	5	0	0	6	1	16.7	11	1	9.1	13	0	0	14	4	28.6	56	7	12.5
RR increase >25% & to a HR<50	7	0	0	5	1	20.0	5	1	20.0	12	1	8.3	11	2	18.2	13	0	0	53	5	9.4
PR (msec)																					
Increase >25% & to a value >200	7	0	0	5	0	0	5	0	0	10	0	0	13	0	0	13	0	0	53	0	0

	80 mg (N=7)			120 mg (N=5)			150 mg (N=6)			200 mg (N=12)			300 mg (N=13)			400 mg (N=14)			All patients (N=57)		
	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%
QRS (msec)																					
Increase >25% and to a value >110	7	0	0	5	0	0	5	1	20.0	12	1	8.3	13	0	0	14	0	0	56	2	3.6

Total is the number of subjects at risk for a specific category. For new abnormality post baseline values, this is the number of subjects with both baseline and post baseline, and baseline not meeting the criteria. For abnormal change from baseline, this is the number of subjects with both baseline and post baseline evaluations.
n is the number of subjects meeting the criteria at least once.
Baseline is defined as the average of all ECG measurements taken at screening.
Change from baseline: post baseline – baseline.
Unscheduled visits are included.

Conclusion:

The following conclusions can be made from this study.

- The MTD of LEQ506 is 400 mg. DLTs included fatigue, dyspnea, and Grade 3 and 4 increases in chemistry laboratory values, including increases in creatine phosphokinase, AST, ALT, and blood uric acid.
- Mean plasma exposure of LEQ506 appeared to increase approximately dose-proportional from 80 mg to 400 mg. The estimated T1/2 of LEQ506 was approximately 1 day.
- Skin Gli1 expression levels showed a trend of correlation with LEQ506 plasma exposure, suggesting a positive PD response and being consistent with the expected mechanism of action of LEQ506.
- LEQ506 was well tolerated. Fatigue, the most common DLT, was also the most common AE, and among the most common SAEs and grade 3/4 AEs.
- The best response of partial response (PR) was observed in 6 subjects in this phase I study.

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Date of Clinical Trial Report

12 Apr 2016