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Sponsor

Novartis

Generic Drug Name

Not applicable.

Trial Indication(s)

Advanced solid tumors

Protocol Number

CLCL161A2104

2009-015594-12 (EUDRACT number)

Protocol Title

A Phase Ib study of LCL161 in combination with weekly paclitaxel in adult patients with advanced solid tumors.

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase II

Study Start/End Dates

12-Apr-2011 to 09-Jan-2015

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

This was an open label, multi-center, Phase Ib dose-escalation study of oral LCL161 administered in combination with weekly paclitaxel (80 mg/m^2/week infused over 1 h) in adult patients with advanced solid tumors.

Centers

7 centers in 4 participating countries (Spain 2; Canada 1; US 3, and Italy 1).

Publication

There are no publications based on this study.

Objectives:

Primary objective

- To determine the maximum tolerated dose (MTD)/recommended dose for expansion (RDE) of LCL161 when administered in combination with once weekly paclitaxel.

Secondary objectives

- To assess the safety and tolerability of the combination, including acute and chronic toxicities;
- To characterize the pharmacokinetics of LCL161 and paclitaxel when administered in combination;
- To describe any preliminary anti-tumor activity associated with this combination treatment;
- To assess target inhibition marker for cell death and cytokines in surrogate and tumor tissue.

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

Paclitaxel (commercially available product, generic paclitaxel was allowed to be used for study treatment): 80 mg/m^2 intravenous, weekly administration (the standard dose used in clinical practice).

LCL161: oral tablets (two strengths: 50 mg and 300 mg) administered immediately following paclitaxel infusion.

Statistical Methods

An adaptive Bayesian logistic regression models (BLRM) guided by the escalation with overdose control (EWOC) principle were used to make dose recommendations and estimate the MTD during the dose-escalation phase of the study. Only observations in Cycle 1 were considered for updating the models. The primary analysis method was an adaptive 3-parameter Bayesian model guided by the escalation with EWOC principle. The secondary analysis method was a 2-parameter Bayesian logistic regression model guided by the EWOC principle, which further controls adverse events (grade 3 or more) related to cytokine release syndrome. The EWOC mandated that any dose of LCL161 in combination with the standard, fixed dose of paclitaxel that has more than a 25% chance of being in the unacceptable toxicity interval (in any one of the two analyses) was not considered for the next dose cohort. The dose recommended was the minimum of the doses recommended from the two analyses.

PK parameters were calculated based on each individual plasma concentration-time profile of patients in pharmacokinetics analysis set.

Preliminary tumor activity was assessed using Investigator read computed tomography/magnetic resonance imaging assessments evaluated under RECIST ver. 1.0. No interim analysis has been planned and performed.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria:

Male or female patients 18 years or older with breast cancer, and an Eastern Cooperative Oncology Group (ECOG) performance status 0-1, had to have a histologically or cytologically confirmed diagnosis of disease that had metastasized or was resistant to therapy. During the dose escalation period, the population consisted of adult patients with solid tumors. During the safety expansion phase, tumor types were restricted to breast cancer or ovarian cancer.

Key exclusion criteria:

- For patients with breast cancer:
  a. Concurrent Her2-directed or anti-estrogen therapy
- For patients with ovarian cancer:
  a. Primary refractory disease, defined as progression during initial treatment with a platinum- and taxane-containing regimen.
  b. Prior treatment with weekly paclitaxel.
  c. More than two chemotherapy regimens given in the relapse setting.
  d. Evidence of a documented bowel obstruction within six months of study entry
- Patients with primary central nervous system tumors or brain metastases. However, if radiation therapy and/or surgery have been completed and serial evaluation by computed tomography (with contrast enhancement) or magnetic resonance imaging (MRI) over a minimum of three months demonstrates stable disease, then the patient may be enrolled. Such patients must have no need for treatment with corticosteroids or enzyme-inducing anti-epileptic medications for their central nervous system disease.

In addition, patients were excluded if they had any concurrent severe and/or uncontrolled medical conditions that could increase the patient's risk for toxicity while in the study or that could confound discrimination between disease and study treatment-related toxicities or impairment of gastrointestinal (GI) function or GI disease that might have significantly altered the absorption of LCL161. Also excluded were patients with impaired cardiac function or clinically significant cardiac or clinically significant pulmonary diseases.

Participant Flow Table

Patient Disposition by treatment (Full analysis set)

Disposition Reason	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Patients treated					

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Disposition Reason	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Treatment discontinued	3 (100)	5 (100)	5 (100)	63 (100)	76 (100)
Primary reason for end of treatment					
Adverse Event(s)	0	1 (20.0)	0	14 (22.2)	15 (19.7)
Subject withdrew consent	0	0	0	6 (9.5)	6 (7.9)
Lost to follow-up	0	0	1 (20.0)	0	1 (1.3)
Administrative problems	0	0	0	1 (1.6)	1 (1.3)
Death	0	0	0	2 (3.2)	2 (2.6)
Disease progression	3 (100)	4 (80.0)	4 (80.0)	40 (63.5)	51 (67.1)
Primary reason for study evaluation completion					
Adverse Event(s)	0	1 (20.0)	0	5 (7.9)	6 (7.9)
Subject withdrew consent	0	0	0	4 (6.3)	4 (5.3)
Lost to follow-up	0	0	1 (20.0)	0	1 (1.3)
Death	0	0	1 (20.0)	4 (6.3)	5 (6.6)
New cancer therapy	0	0	0	5 (7.9)	5 (6.6)
Disease progression	3 (100)	2 (40.0)	0	15 (23.8)	20 (26.3)
F/u phase compl as per prot.	0	2 (40.0)	3 (60.0)	30 (47.6)	35 (46.1)

Study evaluation completion corresponds to the evaluation performed 30-day following treatment discontinuation.

Baseline Characteristics (Full analysis set)

	600 mg LCL161 + Paclitaxel N=3	1200 mg LCL161 + Paclitaxel N=5	1500 mg LCL161 + Paclitaxel N=5	1800 mg LCL161 + Paclitaxel N=63	All patients N=76

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	600 mg LCL161 + Paclitaxel	1200 mg LCL161 + Paclitaxel	1500 mg LCL161 + Paclitaxel	1800 mg LCL161 + Paclitaxel	All patients
	N=3	N=5	N=5	N=63	N=76
Age (Years)					
N	3	5	5	63	76
Mean	47.0	55.0	55.4	57.5	56.8
SD	9.54	8.25	10.60	11.68	11.37
Median	52.0	55.0	54.0	59.0	58.0
Minimum	36.0	45.0	42.0	33.0	33.0
Maximum	53.0	65.0	67.0	78.0	78.0
Age category (Years) -n (%)					
<65	3 (100)	4 (80.0)	3 (60.0)	43 (68.3)	53 (69.7)
65 - <85	0	1 (20.0)	2 (40.0)	20 (31.7)	23 (30.3)
Sex -n (%)					
Male	0	2 (40.0)	3 (60.0)	7 (11.1)	12 (15.8)
Female	3 (100)	3 (60.0)	2 (40.0)	56 (88.9)	64 (84.2)
Race -n (%)					
Caucasian	2 (66.7)	5 (100)	4 (80.0)	56 (88.9)	67 (88.2)
Black	1 (33.3)	0	0	2 (3.2)	3 (3.9)
Asian	0	0	1 (20.0)	4 (6.3)	5 (6.6)
Other	0	0	0	1 (1.6)	1 (1.3)
Ethnicity -n (%)					
Hispanic/Latino	0	3 (60.0)	3 (60.0)	25 (39.7)	31 (40.8)
Chinese	0	0	0	1 (1.6)	1 (1.3)
Japanese	0	0	0	1 (1.6)	1 (1.3)
Mixed Ethnicity	0	0	0	1 (1.6)	1 (1.3)
Other	3 (100)	2 (40.0)	2 (40.0)	35 (55.6)	42 (55.3)
Weight (kg, at baseline)					

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	600 mg LCL161 + Paclitaxel	1200 mg LCL161 + Paclitaxel	1500 mg LCL161 + Paclitaxel	1800 mg LCL161 + Paclitaxel	All patients
	N=3	N=5	N=5	N=63	N=76
N	3	5	5	63	76
Mean	72.5	73.0	64.8	67.8	68.2
SD	30.06	19.48	5.61	13.54	14.17
Median	70.4	63.6	67.5	66.0	66.1
Minimum	43.6	54.0	58.2	46.0	43.6
Maximum	103.6	100.5	70.0	106.6	106.6
Height (cm, at screening)					
N	3	5	5	63	76
Mean	163.0	170.3	172.3	160.3	161.9
SD	14.12	13.11	7.19	9.19	10.05
Median	157.5	165.1	174.0	160.0	160.0
Minimum	152.4	158.0	162.5	143.0	143.0
Maximum	179.0	190.5	181.0	188.0	190.5
Body surface area (m^2)					
N	3	5	5	63	76
Mean	1.81	1.86	1.77	1.75	1.76
SD	.461	.315	.095	.205	.217
Median	1.78	1.72	1.82	1.71	1.72
Minimum	1.37	1.55	1.65	1.44	1.37
Maximum	2.29	2.31	1.84	2.37	2.37
ECOG performance status -n (%)					
0	3 (100)	3 (60.0)	1 (20.0)	29 (46.0)	36 (47.4)
1	0	2 (40.0)	4 (80.0)	34 (54.0)	40 (52.6)

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	600 mg LCL161 + Paclitaxel	1200 mg LCL161 + Paclitaxel	1500 mg LCL161 + Paclitaxel	1800 mg LCL161 + Paclitaxel	All patients
	N=3	N=5	N=5	N=63	N=76

Body Surface Area (Gehan and George): BSA_{m2} =234.94*(height$_{cm,\ at\ screening}$ **0.422)*(weight$_{kg,\ at\ baseline}$ **0.515)/10000
ECOG 0 - Fully active, able to carry on all pre-disease performance without restriction;
1 - Restricted in physically strenuous activity but ambulatory and able to carry out
Work of a light or sedentary nature, e.g., light house work, office work;
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities.
Up and about more than 50% of waking hours;
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours;
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Summary of Efficacy

Primary Outcome Result(s)

Bayesian estimated posterior probabilities for dose limiting toxicities occurring during the first cycle (Dose Determining Set)

	Posterior probabilities (%) that Pr(DLT) is in interval:					Quantiles		
LCL161 Dose (mg)	0-20%	>20%-35%	>35%-100%	Mean	SD	2.5%	50%	97.5%
600	0.968	0.032	0	0.082	0.053	0.011	0.072	0.209
1200	0.926	0.073	0.001	0.113	0.055	0.031	0.104	0.241
1500	0.859	0.138	0.003	0.136	0.059	0.045	0.128	0.273
1800	0.714	0.264	0.022	0.167	0.075	0.055	0.156	0.343
2100	0.571	0.337	0.092	0.204	0.105	0.062	0.184	0.468
2500	0.443	0.346	0.211	0.256	0.152	0.069	0.217	0.659

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Bayesian estimated posterior probabilities for adverse events related to cytokine release syndrome during the first cycle (Dose Determining Set)

LCL161 Dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval: <15%	15-100%	Mean	SD	Quantiles 2.5%	50%	97.5%
600	0.999	0.001	0.02	0.019	0.001	0.014	0.072
1200	0.995	0.005	0.035	0.027	0.005	0.028	0.107
1500	0.987	0.013	0.045	0.033	0.007	0.036	0.13
1800	0.963	0.037	0.055	0.042	0.008	0.044	0.166
2100	0.923	0.077	0.067	0.056	0.009	0.051	0.215
2500	0.867	0.133	0.083	0.079	0.01	0.06	0.3

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

	600 mg LCL161 + Paclitaxel N=3	1200 mg LCL161 + Paclitaxel N=5	1500mg LCL161 + Paclitaxel N=5	1800 mg LCL161 + Paclitaxel N=63	All patients N=76
Best overall response					
Complete response (CR)	0	0	0	2 (3.2)	2 (2.6)
Partial response (PR)	1 (33.3)	1 (20.0)	0	19 (30.2)	21 (27.6)
Stable disease (SDi)	1 (33.3)	2 (40.0)	4 (80.0)	21 (33.3)	28 (36.8)
Progressive disease (PD)	1 (33.3)	2 (40.0)	1 (20.0)	15 (23.8)	19 (25.0)
Unknown	0	0	0	6 (9.5)	6 (7.9)
Overall response rate (ORR)					

	600 mg LCL161 + Paclitaxel N=3	1200 mg LCL161 + Paclitaxel N=5	1500mg LCL161 + Paclitaxel N=5	1800 mg LCL161 + Paclitaxel N=63	All patients N=76
(CR or PR)	1 (33.3)	1 (20.0)	0	21 (33.3)	23 (30.3)
95% CI	(0.8-90.6)	(0.5-71.6)	(0.0-52.2)	(22.0-46.3)	(20.2-41.9)

Secondary Outcome Result(s)

None

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Summary of Safety

Safety Results

Adverse events, regardless of study treatment relationship, by primary system organ class and treatment (Safety set)

Primary system organ class	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
-Total	3 (100)	5 (100)	5 (100)	63 (100)	76 (100)
Gastrointestinal disorders	3 (100)	5 (100)	4 (80.0)	56 (88.9)	68 (89.5)
General disorders and administration site Conditions	3 (100)	4 (80.0)	4 (80.0)	52 (82.5)	63 (82.9)
Blood and lymphatic system disorders	2 (66.7)	4 (80.0)	2 (40.0)	54 (85.7)	62 (81.6)
Skin and subcutaneous tissue disorders	2 (66.7)	5 (100)	4 (80.0)	39 (61.9)	50 (65.8)
Nervous system disorders	3 (100)	3 (60.0)	2 (40.0)	40 (63.5)	48 (63.2)
Respiratory, thoracic and mediastinal disorders	1 (33.3)	2 (40.0)	2 (40.0)	38 (60.3)	43 (56.6)
Infections and infestations	2 (66.7)	1 (20.0)	3 (60.0)	30 (47.6)	36 (47.4)
Metabolism and nutrition disorders	2 (66.7)	2 (40.0)	0	30 (47.6)	34 (44.7)
Musculoskeletal and connective tissue disorders	2 (66.7)	3 (60.0)	1 (20.0)	24 (38.1)	30 (39.5)
Investigations	1 (33.3)	1 (20.0)	2 (40.0)	19 (30.2)	23 (30.3)
Vascular disorders	1 (33.3)	2 (40.0)	1 (20.0)	15 (23.8)	19 (25.0)
Psychiatric disorders	1 (33.3)	2 (40.0)	0	12 (19.0)	15 (19.7)
Eye disorders	1 (33.3)	1 (20.0)	0	8 (12.7)	10 (13.2)
Injury, poisoning and procedural complications	0	1 (20.0)	1 (20.0)	8 (12.7)	10 (13.2)
Renal and urinary disorders	1 (33.3)	0	0	8 (12.7)	9 (11.8)
Immune system disorders	0	1 (20.0)	0	6 (9.5)	7 (9.2)

Primary system organ class	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Reproductive system and breast disorders	0	0	0	6 (9.5)	6 (7.9)
Ear and labyrinth disorders	1 (33.3)	0	0	3 (4.8)	4 (5.3)
Hepatobiliary disorders	1 (33.3)	0	1 (20.0)	2 (3.2)	4 (5.3)
Cardiac disorders	0	0	0	2 (3.2)	2 (2.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	1 (1.6)	1 (1.3)

Primary system organ classes are sorted 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 adverse events is counted only once in the total row.
Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Grade 3/4 adverse events, regardless of study treatment relationship, by preferred term and treatment (safety set)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
-Total	3 (100)	3 (60.0)	5 (100)	52 (82.5)	63 (82.9)
Neutropenia	1 (33.3)	1 (20.0)	1 (20.0)	27 (42.9)	30 (39.5)
Anaemia	1 (33.3)	0	0	13 (20.6)	14 (18.4)
Febrile neutropenia	0	0	0	8 (12.7)	8 (10.5)
Asthenia	0	0	0	5 (7.9)	5 (6.6)
Dyspnoea	0	0	0	5 (7.9)	5 (6.6)
Neutrophil count decreased	0	0	2 (40.0)	3 (4.8)	5 (6.6)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Hyponatraemia	0	0	0	4 (6.3)	4 (5.3)
Leukopenia	0	0	0	4 (6.3)	4 (5.3)
Thrombocytopenia	0	0	0	4 (6.3)	4 (5.3)
Aspartate aminotransferase increased	1 (33.3)	0	1 (20.0)	1 (1.6)	3 (3.9)
Fatigue	0	0	0	3 (4.8)	3 (3.9)
Hypokalaemia	0	0	0	3 (4.8)	3 (3.9)
Hypotension	0	0	1 (20.0)	2 (3.2)	3 (3.9)
Pneumonitis	0	0	0	3 (4.8)	3 (3.9)
Sepsis	0	0	0	3 (4.8)	3 (3.9)
Alanine aminotransferase increased	0	0	0	2 (3.2)	2 (2.6)
Ascites	0	0	0	2 (3.2)	2 (2.6)
Diarrhoea	0	0	0	2 (3.2)	2 (2.6)
Gamma-glutamyltransferase increased	0	0	0	2 (3.2)	2 (2.6)
Hyperglycaemia	0	0	0	2 (3.2)	2 (2.6)
Lymphopenia	0	0	0	2 (3.2)	2 (2.6)
Nausea	0	0	0	2 (3.2)	2 (2.6)
Neuropathy peripheral	0	1 (20.0)	0	1 (1.6)	2 (2.6)
Non-cardiac chest pain	0	0	0	2 (3.2)	2 (2.6)
Pneumonia	0	0	0	2 (3.2)	2 (2.6)
Upper respiratory tract infection	0	0	0	2 (3.2)	2 (2.6)
Urinary tract infection	0	0	1 (20.0)	1 (1.6)	2 (2.6)
Vomiting	0	0	0	2 (3.2)	2 (2.6)
White blood cell count decreased	0	0	0	2 (3.2)	2 (2.6)
Abdominal pain	0	0	0	1 (1.6)	1 (1.3)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Anaphylactic reaction	0	0	0	1 (1.6)	1 (1.3)
Anxiety	0	0	0	1 (1.6)	1 (1.3)
Aphasia	0	0	0	1 (1.6)	1 (1.3)
Blood glucose increased	0	0	0	1 (1.6)	1 (1.3)
Chest pain	0	0	0	1 (1.6)	1 (1.3)
Cranial nerve disorder	0	0	0	1 (1.6)	1 (1.3)
Decreased appetite	0	0	0	1 (1.6)	1 (1.3)
Deep vein thrombosis	0	0	0	1 (1.6)	1 (1.3)
Dehydration	1 (33.3)	0	0	0	1 (1.3)
Dental caries	0	0	0	1 (1.6)	1 (1.3)
Drug hypersensitivity	0	0	0	1 (1.6)	1 (1.3)
Emphysema	0	0	0	1 (1.6)	1 (1.3)
Failure to thrive	1 (33.3)	0	0	0	1 (1.3)
Flushing	0	0	1 (20.0)	0	1 (1.3)
Generalised oedema	0	0	0	1 (1.6)	1 (1.3)
Haematuria	0	0	0	1 (1.6)	1 (1.3)
Haemolytic anaemia	0	0	0	1 (1.6)	1 (1.3)
Hepatocellular injury	0	0	1 (20.0)	0	1 (1.3)
Hypertension	0	0	0	1 (1.6)	1 (1.3)
Hypertriglyceridaemia	0	1 (20.0)	0	0	1 (1.3)
Hypoalbuminaemia	0	0	0	1 (1.6)	1 (1.3)
Hypocalcaemia	0	0	0	1 (1.6)	1 (1.3)
Hypophosphataemia	0	0	0	1 (1.6)	1 (1.3)
Intestinal perforation	0	0	0	1 (1.6)	1 (1.3)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Lung infection	0	0	0	1 (1.6)	1 (1.3)
Lung infiltration	0	0	0	1 (1.6)	1 (1.3)
Lymphocyte count decreased	0	0	0	1 (1.6)	1 (1.3)
Lymphoedema	0	0	0	1 (1.6)	1 (1.3)
Mucosal inflammation	0	0	0	1 (1.6)	1 (1.3)
Neurotoxicity	0	0	0	1 (1.6)	1 (1.3)
Overdose	0	0	0	1 (1.6)	1 (1.3)
Pain	0	0	0	1 (1.6)	1 (1.3)
Periorbital oedema	0	0	0	1 (1.6)	1 (1.3)
Peripheral sensory neuropathy	0	0	0	1 (1.6)	1 (1.3)
Peritonitis	0	0	0	1 (1.6)	1 (1.3)
Pulmonary toxicity	0	0	0	1 (1.6)	1 (1.3)
Pulpitis dental	0	0	0	1 (1.6)	1 (1.3)
Pyramidal tract syndrome	0	0	0	1 (1.6)	1 (1.3)
Pyrexia	1 (33.3)	0	0	0	1 (1.3)
Rash pruritic	0	0	0	1 (1.6)	1 (1.3)
Rectal haemorrhage	0	0	0	1 (1.6)	1 (1.3)
Skin infection	0	0	0	1 (1.6)	1 (1.3)
Small intestinal obstruction	0	0	0	1 (1.6)	1 (1.3)
Stomatitis	0	0	1 (20.0)	0	1 (1.3)
Tooth infection	0	0	1 (20.0)	0	1 (1.3)
Urinary incontinence	0	0	0	1 (1.6)	1 (1.3)
Vaginal lesion	0	0	0	1 (1.6)	1 (1.3)
Venous thrombosis	0	0	0	1 (1.6)	1 (1.3)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Wound complication	0	0	0	1 (1.6)	1 (1.3)

Preferred terms are sorted 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 adverse events is counted only once in the total row.
Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Serious adverse events, regardless of study treatment relationship, by preferred term and treatment (Safety set)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
-Total	3 (100)	1 (20.0)	2 (40.0)	35 (55.6)	41 (53.9)
Febrile neutropenia	0	0	0	8 (12.7)	8 (10.5)
Neutropenia	0	1 (20.0)	0	5 (7.9)	6 (7.9)
Pyrexia	1 (33.3)	0	0	5 (7.9)	6 (7.9)
Dyspnoea	0	0	0	3 (4.8)	3 (3.9)
Pneumonitis	0	0	0	3 (4.8)	3 (3.9)
Sepsis	0	0	0	3 (4.8)	3 (3.9)
Alanine aminotransferase increased	0	0	1 (20.0)	1 (1.6)	2 (2.6)
Hypotension	0	0	0	2 (3.2)	2 (2.6)
Pneumonia	0	0	0	2 (3.2)	2 (2.6)
Urinary tract infection	1 (33.3)	0	1 (20.0)	0	2 (2.6)
Vomiting	0	0	0	2 (3.2)	2 (2.6)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Abdominal pain	0	0	0	1 (1.6)	1 (1.3)
Anaphylactic reaction	0	0	0	1 (1.6)	1 (1.3)
Ascites	0	0	0	1 (1.6)	1 (1.3)
Aspartate aminotransferase increased	0	0	1 (20.0)	0	1 (1.3)
Asthenia	0	0	0	1 (1.6)	1 (1.3)
Cerebral ischaemia	0	0	0	1 (1.6)	1 (1.3)
Chest pain	0	0	0	1 (1.6)	1 (1.3)
Cranial nerve disorder	0	0	0	1 (1.6)	1 (1.3)
Decreased appetite	0	0	0	1 (1.6)	1 (1.3)
Deep vein thrombosis	0	0	0	1 (1.6)	1 (1.3)
Emphysema	0	0	0	1 (1.6)	1 (1.3)
Failure to thrive	1 (33.3)	0	0	0	1 (1.3)
Generalised oedema	0	0	0	1 (1.6)	1 (1.3)
Haematuria	0	0	0	1 (1.6)	1 (1.3)
Herpes virus infection	0	0	0	1 (1.6)	1 (1.3)
Hypocalcaemia	0	0	0	1 (1.6)	1 (1.3)
Hypokalaemia	0	0	0	1 (1.6)	1 (1.3)
Hyponatraemia	0	0	0	1 (1.6)	1 (1.3)
Intestinal perforation	0	0	0	1 (1.6)	1 (1.3)
Lung infection	0	0	0	1 (1.6)	1 (1.3)
Lung infiltration	0	0	0	1 (1.6)	1 (1.3)
Lymphoedema	0	0	0	1 (1.6)	1 (1.3)
Mucosal inflammation	0	0	0	1 (1.6)	1 (1.3)
Nausea	0	0	0	1 (1.6)	1 (1.3)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Overdose	0	0	0	1 (1.6)	1 (1.3)
Pain	0	0	0	1 (1.6)	1 (1.3)
Rash pustular	0	0	0	1 (1.6)	1 (1.3)
Rectal haemorrhage	0	0	0	1 (1.6)	1 (1.3)
Skin infection	0	0	0	1 (1.6)	1 (1.3)
Small intestinal obstruction	0	0	0	1 (1.6)	1 (1.3)
Tooth infection	0	0	1 (20.0)	0	1 (1.3)
Upper respiratory tract infection	0	0	0	1 (1.6)	1 (1.3)
Urinary incontinence	0	0	0	1 (1.6)	1 (1.3)
Urosepsis	0	0	0	1 (1.6)	1 (1.3)
Vaginal lesion	0	0	0	1 (1.6)	1 (1.3)
Venous thrombosis	0	0	0	1 (1.6)	1 (1.3)
White blood cell count decreased	0	0	0	1 (1.6)	1 (1.3)
Wound complication	0	0	0	1 (1.6)	1 (1.3)

Preferred terms are sorted 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 adverse events is counted only once in the total row.
Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Deaths, on-treatment or within 30 days after the last dose of study drug, by preferred term and dosing regimen

Dose cohort	Principal cause of death	Date of last dose	Date of death
INC280 1800 mg + paclitaxel	Neoplasm	06-Feb-2014	04-Mar-2014
INC280 1800 mg + paclitaxel	Neoplasm	27-Feb-2012	19-Mar-2012
INC280 1800 mg + paclitaxel	Febrile neutropenia	26-Jun-2012	01-Jul-2012

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Dose cohort	Principal cause of death	Date of last dose	Date of death
INC280 1800 mg + paclitaxel	Intestinal perforation	27-May-2014	30-May-2014

Adverse events leading to study drug discontinuation, regardless of study treatment relationship, by primary preferred term and treatment (Safety set)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
-Total	0	1 (20.0)	0	16 (25.4)	17 (22.4)
Peripheral sensory neuropathy	0	0	0	3 (4.8)	3 (3.9)
Asthenia	0	0	0	2 (3.2)	2 (2.6)
Neuropathy peripheral	0	1 (20.0)	0	1 (1.6)	2 (2.6)
Neutropenia	0	0	0	2 (3.2)	2 (2.6)
Sepsis	0	0	0	2 (3.2)	2 (2.6)
Anaphylactic reaction	0	0	0	1 (1.6)	1 (1.3)
Aphasia	0	0	0	1 (1.6)	1 (1.3)
Bradyphrenia	0	0	0	1 (1.6)	1 (1.3)
Cerebral ischaemia	0	0	0	1 (1.6)	1 (1.3)
Dizziness	0	0	0	1 (1.6)	1 (1.3)
Febrile neutropenia	0	0	0	1 (1.6)	1 (1.3)
Haemolytic anaemia	0	0	0	1 (1.6)	1 (1.3)
Infusion related reaction	0	0	0	1 (1.6)	1 (1.3)
Intestinal perforation	0	0	0	1 (1.6)	1 (1.3)
Pneumonitis	0	0	0	1 (1.6)	1 (1.3)
Pyramidal tract syndrome	0	0	0	1 (1.6)	1 (1.3)
Pyrexia	0	0	0	1 (1.6)	1 (1.3)
Rash	0	0	0	1 (1.6)	1 (1.3)

Preferred term	600 mg LCL161 + Paclitaxel N=3 n (%)	1200 mg LCL161 + Paclitaxel N=5 n (%)	1500 mg LCL161 + Paclitaxel N=5 n (%)	1800 mg LCL161 + Paclitaxel N=63 n (%)	All patients N=76 n (%)
Preferred terms are sorted 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 adverse events within a primary system organ class is counted only once in the total row. Only AEs occurring during treatment or within 30 days of the last study medication are reported.					

Other Relevant Findings

Summary of pharmacokinetic parameters for LCL161 following Cycle 1 Day 1, by treatment (Pharmacokinetic Analysis set)

Treatment	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	CL/F (L/h)	Vz/F (L)	T1/2 (h)
600 mg LCL161 + Paclitaxel (80 mg/m^2)	N	3	3	3	3	3	3	3
	Mean (SD)	1717 (552)		24664 (11111)	24737 (11199)	27.24 (9.926)	296.77 (84.486)	
	CV% mean	32.1		45.1	45.3	36.4	28.5	
	Geo-mean	1663		23188	23244	25.81	287.60	
	CV% geo-mean	31.0		43.7	44.0	44.0	32.6	
	Median	1460	4.02	19219	19245	31.18	343.23	7.63
	[Min; Max]	[1340; 2350]	[4.00; 4.05]	[17325; 37447]	[17345; 37622]	[15.95; 34.59]	[199.25; 347.84]	[6.97; 8.66]
1200 mg LCL161 + Paclitaxel (80 mg/m^2)	N	5	5	5	5	5	5	5

Treatment	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	CL/F (L/h)	Vz/F (L)	T1/2 (h)
	Mean (SD)	1864 (417)		24320 (3932)	24370 (3924)	50.21 (7.568)	524.15 (113.567)	
	CV% mean	22.4		16.2	16.1	15.1	21.7	
	Geo-mean	1827		24077	24129	49.73	514.35	
	CV% geo-mean	22.7		15.8	15.7	15.7	22.0	
	Median	1700	4.00	23142	23274	51.56	489.77	6.98
	[Min; Max]	[1400; 2320]	[1.00; 8.00]	[20455; 30247]	[20467; 30273]	[39.64; 58.63]	[385.01; 679.88]	[6.39; 8.52]
1500 mg LCL161 + Paclitaxel (80 mg/m^2)	N	4	4	4	4	4	4	4
	Mean (SD)	2348 (1074)		29204 (10639)	29544 (10830)	57.11 (23.778)	633.97 (253.147)	
	CV% mean	45.8		36.4	36.7	41.6	39.9	
	Geo-mean	2124		27630	27927	53.71	596.99	
	CV% geo-mean	59.3		41.1	41.5	41.5	41.6	
	Median	2545	4.00	29697	30001	51.31	584.65	7.70
	[Min; Max]	[1010; 3290]	[3.95; 7.98]	[16722; 40698]	[16736; 41439]	[36.20; 89.63]	[423.80; 942.80]	[6.91; 8.61]
1800 mg LCL161 + Paclitaxel (80 mg/m^2)	N	30	30	30	30	30	30	30
	Mean (SD)	2463 (1139)		34374 (16079)	34512 (16121)	63.24 (30.158)	710.26 (323.548)	
	CV% mean	46.3		46.8	46.7	47.7	45.6	
	Geo-mean	2250		31249	31374	57.37	641.35	

Treatment	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	CL/F (L/h)	Vz/F (L)	T1/2 (h)
	CV% geo-mean	45.0		46.8	46.9	46.9	50.3	
	Median	2295	3.99	31417	31482	57.18	591.15	7.62
	[Min; Max]	[766; 6420]	[1.00; 8.00]	[11841; 91192]	[11848; 91211]	[19.73; 151.92]	[153.64; 1502.79]	[5.40; 12.43]

Summary of pharmacokinetic parameters of paclitaxel following Cycle 1 Day 1, by treatment (Pharmacokinetic Analysis set)

Treatment	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	CL (L/h)	Vz (L)	T1/2 (h)
600 mg LCL161 + Paclitaxel (80 mg/m^2)	N	3	3	3	3	3	3	3
	Mean (SD)	3440 (1039)		6358 (1330)	6599 (1355)	22.68 (9.079)	414.65 (180.549)	
	CV% mean	30.2		20.9	20.5	40.0	43.5	
	Geo-mean	3321		6270	6512	21.39	385.81	
	CV% geo-mean	34.6		20.3	19.9	45.1	51.0	
	Median	3840	0.98	5829	6028	22.89	425.38	12.88
	[Min; Max]	[2260; 4220]	[0.92; 1.17]	[5373; 7871]	[5623; 8146]	[13.50; 31.66]	[228.98; 589.60]	[11.75; 12.91]
1200 mg LCL161 + Paclitaxel (80 mg/m^2)	N	5	5	5	5	5	5	5
	Mean (SD)	2688 (1281)		5075 (2270)	5237 (2345)	32.91 (16.175)	583.86 (327.259)	
	CV% mean	47.6		44.7	44.8	49.2	56.1	
	Geo-mean	2473		4734	4886	29.73	513.68	

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Treatment	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	CL (L/h)	Vz (L)	T1/2 (h)
	CV% geo-mean	46.8		42.1	41.9	54.8	61.9	
	Median	1860	1.07	4476	4581	27.07	415.15	11.96
	[Min; Max]	[1710; 4610]	[1.00; 1.47]	[3178; 8846]	[3295; 9148]	[14.98; 55.54]	[251.21; 1053.22]	[10.63; 13.14]
1500 mg LCL161 + Paclitaxel (80 mg/m^2)	N	5	5	5	5	5	5	5
	Mean (SD)	2154 (684)		4701 (1121)	4923 (1172)	29.96 (8.281)	592.66 (187.276)	
	CV% mean	31.8		23.9	23.8	27.6	31.6	
	Geo-mean	2064		4591	4809	29.13	571.21	
	CV% geo-mean	33.9		25.1	24.8	26.4	30.4	
	Median	1930	1.00	4591	4765	29.03	540.99	14.06
	[Min; Max]	[1320; 2900]	[1.00; 1.17]	[3201; 6227]	[3391; 6559]	[22.11; 43.35]	[430.47; 886.54]	[12.11; 15.68]
1800 mg LCL161 + Paclitaxel (80 mg/m^2)	N	31	31	31	31	31	31	31
	Mean (SD)	2558 (1134)		4992 (1833)	5228 (1878)	29.71 (9.795)	606.81 (234.463)	
	CV% mean	44.3		36.7	35.9	33.0	38.6	
	Geo-mean	2336		4711	4943	28.08	558.48	
	CV% geo-mean	45.8		34.9	34.3	36.2	45.6	
	Median	2490	1.08	4654	4811	28.78	608.45	13.49
	[Min; Max]	[856; 5690]	[0.98; 1.32]	[2688; 9779]	[2828; 10079]	[12.60; 52.70]	[202.16; 1100.65]	[10.95; 17.76]

Conclusion:

A total of 76 patients were enrolled and treated on the study. Considering the overall tolerability of each of the two compounds, the recommended dose for expansion was declared as LCL161 (1800 mg)/paclitaxel (80 mg/m^2) based on the 23 patients treated in the dose escalation phase. Based on experiences with previous studies, doses of LCL161 higher than 1800 mg were not explored. Therefore the maximum tolerated dose was not determined. Sixty-three patients were enrolled and treated in the expansion phase at the recommended dose for expansion of LCL161(1800 mg)/paclitaxel (80 mg/m^2).

At the recommended dose for expansion (LCL161 [1800 mg]/paclitaxel [80 mg/m^2]), tolerability was marginal with 16 patients (25.4%) discontinuing study treatment for adverse events. No single adverse event accounted for the majority of treatment discontinuations. Despite the rate of discontinuation, a significant signal was observed in patients with ovarian cancer with an overall response rate of approximately 30% in a patient population where standard therapies are expected to produce a response rate well under 20%. Evidence for a pharmacokinetic-interaction was not observed between LCL161 and paclitaxel. Based on these data, further exploration of this combination may be warranted to define a better tolerated dose and/or schedule that could be explored further in ovarian cancer and potentially other indications.

Date of Clinical Trial Report

Jan-6-2016