Clinical trial results:
A Phase II, multi-center, open-label, neoadjuvant, randomized study of weekly paclitaxel with or without LCL161 in patients with triple negative breast cancer

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2012-000677-23
Trial protocol	GB ES IE IT BE CZ DE
Global end of trial date	18 September 2014

Results information

Result version number	v1 (current)
This version publication date	18 July 2018
First version publication date	18 July 2018

Trial information

Trial identification

Sponsor protocol code	CLCL161A2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01617668
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 61324111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether adding LCL161 to weekly paclitaxel enhances the efficacy of paclitaxel in women with TNBC, analyzed separately in the gene expression signature negative and positive groups.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	209
EEA total number of subjects	106

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	194
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

215 patients were randomized to receive the study treatment. 105 gene expression signature positive patients were randomized to LCL161+paclitaxel (N=51) or paclitaxel only (N=54). 110 gene expression signature negative patients were randomized to LCL161+paclitaxel (N=55) or paclitaxel only (N=55).

Pre-assignment

Screening details:

Only 50 of 54 pts in the Paclitaxel without LCL161 (Positive group) received study drug; Only 53 of 55 pts in the Paclitaxel without LCL161 (Negative group) received study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Paclitaxel with LCL161 (Positive group)

Arm description:

Patients who were gene signature positive were randomized to the experimental arm received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	LCL161
Investigational medicinal product code	LCL161
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LCL161 (1800 mg once weekly) was supplied as film-coated tablets of 300 mg strength and was administered orally and was given for 12 weeks.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was given as 80 mg/m2 weekly and was administered as infusion.

Arm title	Paclitaxel without LCL161 (Positive group)

Arm description:

Patients who were gene signature positive were randomized to the control arm received paclitaxel 80 mg/m2 weekly for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was given as 80 mg/m2 weekly and was administered as infusion.

Arm title	Paclitaxel with LCL161 (Negative group)

Arm description:

Patients who were gene signature negative were randomized to the experimental arm received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	LCL161
Investigational medicinal product code	LCL161
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LCL161 (1800 mg once weekly) was supplied as film-coated tablets of 300 mg strength and was administered orally and was given for 12 weeks.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was given as 80 mg/m2 weekly and was administered as infusion.

Arm title	Paclitaxel without LCL161 (Negative group)

Arm description:

Patients who were gene signature negative were randomized to the control arm received paclitaxel 80 mg/m2 weekly for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was given as 80 mg/m2 weekly and was administered as infusion.

Number of subjects in period 1	Paclitaxel with LCL161 (Positive group)	Paclitaxel without LCL161 (Positive group)	Paclitaxel with LCL161 (Negative group)
Started	51	50	55
Completed	38	41	32
Not completed	13	9	23
Physician decision	1	2	3
Adverse event, non-fatal	7	-	12
Progressive Disease	4	4	6
Subject/guardian decision	1	3	2

Number of subjects in period 1	Paclitaxel without LCL161 (Negative group)
Started	53

Completed	38
Not completed	15
Physician decision	-
Adverse event, non-fatal	5
Progressive Disease	9
Subject/guardian decision	1

Baseline characteristics

Reporting groups	
Reporting group title	Paclitaxel with LCL161 (Positive group)
Reporting group description:	
Patients who were gene signature positive were randomized to the experimental arm received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks.	
Reporting group title	Paclitaxel without LCL161 (Positive group)
Reporting group description:	
Patients who were gene signature positive were randomized to the control arm received paclitaxel 80 mg/m2 weekly for 12 weeks.	
Reporting group title	Paclitaxel with LCL161 (Negative group)
Reporting group description:	
Patients who were gene signature negative were randomized to the experimental arm received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks.	
Reporting group title	Paclitaxel without LCL161 (Negative group)
Reporting group description:	
Patients who were gene signature negative were randomized to the control arm received paclitaxel 80 mg/m2 weekly for 12 weeks.	

Reporting group values	Paclitaxel with LCL161 (Positive group)	Paclitaxel without LCL161 (Positive group)	Paclitaxel with LCL161 (Negative group)
Number of subjects	51	50	55
Age, Customized Units: Participants			
< 65 years	46	46	52
>= 65 years	5	4	3
Age Continuous Units: Years			
arithmetic mean	49.4	48.4	47.8
standard deviation	± 9.83	± 11.08	± 10.46
Gender, Male/Female Units: Participants			
Female	51	50	55
Male	0	0	0

Reporting group values	Paclitaxel without LCL161 (Negative group)	Total	
Number of subjects	53	209	
Age, Customized Units: Participants			
< 65 years	50	194	
>= 65 years	3	15	
Age Continuous Units: Years			
arithmetic mean	49		
standard deviation	± 8.92	-	
Gender, Male/Female Units: Participants			
Female	53	209	

Male	0	0	

End points

End points reporting groups

Reporting group title	Paclitaxel with LCL161 (Positive group)

Reporting group description:

Patients who were gene signature positive were randomized to the experimental arm received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks.

Reporting group title	Paclitaxel without LCL161 (Positive group)

Reporting group description:

Patients who were gene signature positive were randomized to the control arm received paclitaxel 80 mg/m2 weekly for 12 weeks.

Reporting group title	Paclitaxel with LCL161 (Negative group)

Reporting group description:

Patients who were gene signature negative were randomized to the experimental arm received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks.

Reporting group title	Paclitaxel without LCL161 (Negative group)

Reporting group description:

Patients who were gene signature negative were randomized to the control arm received paclitaxel 80 mg/m2 weekly for 12 weeks.

Subject analysis set title	FAS: LCL161 + Paclitaxel (gene expression signature positive)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) was composed of all patients who received at least one full or partial dose of LCL161 + paclitaxel or one full or partial dose of paclitaxel alone. Unless otherwise specified, patients were classified according to treatment arm assigned (two randomized treatment arms) and gene expression signature status (positive or negative) determined at randomization as reported in interactive voice response system (IVRS).

Patients randomized to the experimental arm for gene expression signature positive received LCL161 1800 mg once weekly + paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	FAS: Paclitaxel only (gene expression signature positive)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients randomized to the control arm for gene expression signature positive received paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS1: LCL161 + Paclitaxel (gene expression signature negative)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the experimental arm for gene expression signature negative received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	FAS: Paclitaxel only (gene expression signature negative)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients randomized to the control arm for gene expression signature negative received paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS1: LCL161 + Paclitaxel
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Efficacy Analysis Set 1 (EAS1) was composed of all patients who receive at least one full or partial dose of LCL161 + paclitaxel or one full or partial dose of paclitaxel alone with a valid gene expression signature score. Patients were classified according to treatment received and gene expression signature status derived from the continuous score. Patients with the gene expression signature score of 0.6661

or higher were classified in a gene expression signature positive group. Patients with a score below 0.6661 were classified as gene expression signature negative.

Patients randomized to the experimental arm who received LCL161 1800 mg once weekly + paclitaxel 80 mg/m2 weekly for 12 weeks.

Subject analysis set title	EAS1: Paclitaxel only
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the control arm who received paclitaxel 80 mg/m2 weekly for 12 weeks.

Subject analysis set title	EAS1: LCL161 + Paclitaxel (gene expression signature positive)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the experimental arm for gene expression signature positive received LCL161 1800 mg once weekly + paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS1: Paclitaxel only (gene expression signature positive)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the control arm for gene expression signature positive received paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS1: Paclitaxel only (gene expression signature negative)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the control arm for gene expression signature negative received paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS1: LCL161 + Paclitaxel (gene expression signature positive)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the experimental arm for gene expression signature positive received LCL161 1800 mg once weekly + paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS1: Paclitaxel only (gene expression signature positive)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the control arm for gene expression signature positive received paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS1: LCL161 + Paclitaxel (gene expression signature negative)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the experimental arm for gene expression signature negative received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS1: Paclitaxel only (gene expression signature negative)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the control arm for gene expression signature negative received paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS2: LCL161 + Paclitaxel (gene expression signature positive)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Efficacy Analysis Set 2 (EAS2) was the same as EAS1 except that the threshold for classifying a patient into the positive gene group was 0.7716. Patients with the gene expression signature score of 0.7716 or higher were classified in a gene expression signature

positive group. Patients with a score below 0.7716 were classified as gene expression signature negative.

Patients randomized to the experimental arm for gene expression signature positive received LCL161 1800 mg once weekly + paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS2: Paclitaxel only (gene expression signature positive)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the control arm for gene expression signature positive received paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS2: LCL161 + Paclitaxel (gene expression signature negative)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the experimental arm for gene expression signature negative received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	EAS2: Paclitaxel only (gene expression signature negative)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomized to the control arm for gene expression signature negative received paclitaxel 80 mg/m2 weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	PAS: LCL161 + Paclitaxel (gene expression signature negative)
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients randomized to the experimental arm for gene expression signature negative received paclitaxel 80 mg/m2 weekly + LCL161 1800 mg once weekly for 12 weeks. Equal numbers of patients with gene expression signature positive and negative disease were included in each treatment arm.

Subject analysis set title	PAS: LCL161
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients randomized to the LCL161 1800 mg once weekly for 12 weeks.

Primary: Pathological complete response (pCR) rate in breast after 12 weeks of therapy

End point title	Pathological complete response (pCR) rate in breast after 12 weeks of therapy

End point description:

pCR rate was defined as histopathologically confirmed absence of invasive disease in the breast. To assess whether adding LCL161 to weekly paclitaxel enhances the efficacy of paclitaxel in women with triple negative breast cancer. Analyses were performed separately in the gene expression signature negative and positive groups. This analysis was based on Bayesian design using a binomial distribution for the data with a beta prior. The method of dispersion used in this study is Credible Interval (Crl) and not Confidence Interval (CI). Median values are posterior medians of pCR rate for each group.

End point type	Primary

End point timeframe:

12 weeks

End point values	Paclitaxel with LCL161 (Positive group)	Paclitaxel without LCL161 (Positive group)	Paclitaxel with LCL161 (Negative group)	Paclitaxel without LCL161 (Negative group)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	50	55	53
Units: Percentage of Participants				
median (confidence interval 95%)	24.9 (14.5 to 37.8)	23.4 (13.3 to 36.2)	6.9 (2.2 to 15.5)	9.1 (3.3 to 18.6)

Statistical analyses

Statistical analysis title	Difference - pCR rate (%) within signature -ve grp
Comparison groups	Paclitaxel with LCL161 (Negative group) v Paclitaxel without LCL161 (Negative group)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Posterior med. diff -pCR rate b/w groups
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	8.3

Statistical analysis title	Difference - pCR rate (%) within signature +ve grp
Comparison groups	Paclitaxel with LCL161 (Positive group) v Paclitaxel without LCL161 (Positive group)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Posterior med. diff -pCR rate b/w groups
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	18

Primary: Number of participants with Pathological complete response (pCR) in breast after 12 weeks of therapy

End point title	Number of participants with Pathological complete response (pCR) in breast after 12 weeks of therapy[1]

End point description:

To assess the number of patients who experienced a pathological response in breast. No statistical hypothesis test was done.

End point type	Primary

End point timeframe:

12 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical hypothesis test was done for this endpoint.

End point values	Paclitaxel with LCL161 (Positive group)	Paclitaxel without LCL161 (Positive group)	Paclitaxel with LCL161 (Negative group)	Paclitaxel without LCL161 (Negative group)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	50	55	53
Units: Participants	13	12	4	5

Statistical analyses

No statistical analyses for this end point

Primary: Difference in pCR rates between treatment arms

End point title	Difference in pCR rates between treatment arms[2]

End point description:

pCR rate was defined as histopathologically confirmed absence of invasive disease in the breast. To assess whether adding LCL161 to weekly paclitaxel enhances the efficacy of paclitaxel in women with triple negative breast cancer. Analyses were performed separately in the gene expression signature negative and positive groups. This analysis was based on the posterior distribution of the difference in pCR rates between the experimental and control arms of the study, within each gene expression signature group. The measure median was used as these values are medians of posterior distribution of difference of pCR rate between treatment arms based on a Bayesian model. 95% Confidence interval is actually 95% credible interval. No statistical hypothesis test was done.

End point type	Primary

End point timeframe:

12 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical hypothesis test was done for this endpoint.

End point values	Paclitaxel with LCL161 (Positive group)	Paclitaxel without LCL161 (Positive group)	Paclitaxel with LCL161 (Negative group)	Paclitaxel without LCL161 (Negative group)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	50	55	53
Units: Difference in PCR Rate				
median (confidence interval 95%)	1.5 (-15 to 18)	999.99 (99.99 to 9999.99)	-2 (-12.7 to 8.3)	999.99 (99.99 to 9999.99)

Statistical analyses

No statistical analyses for this end point

Secondary: Posterior distribution of difference in pCR rates between gene expression signature groups (EAS1)

End point title	Posterior distribution of difference in pCR rates between gene expression signature groups (EAS1)

End point description:

To assess whether use of the gene expression signature identifies tumors more likely to respond to treatment with LCL161 and paclitaxel. The measure median was used as these values are medians of posterior distribution of difference of pCR rate between gene signature positive and gene signature negative groups based on a Bayesian model. 95% Confidence interval is actually 95% credible interval.

End point type	Secondary

End point timeframe:

12 weeks

End point values	EAS1: LCL161 + Paclitaxel			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: Difference in pCR rate				
median (confidence interval 95%)	18.2 (5 to 32.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Posterior distribution of difference in pCR rates between gene expression groups within treatment (EAS1)

End point title	Posterior distribution of difference in pCR rates between gene expression groups within treatment (EAS1)

End point description:

To assess whether use of the gene expression signature identifies tumors more likely to respond to treatment with paclitaxel only. The measure median was used as these values are medians of posterior distribution of difference of pCR rate between gene signature positive and gene signature negative groups based on a Bayesian model. 95% Confidence interval is actually 95% credible interval.

End point type	Secondary

End point timeframe:

12 weeks

End point values	EAS1: Paclitaxel only			
Subject group type	Subject analysis set			
Number of subjects analysed	102			
Units: Difference in pCR rate				
median (confidence interval 95%)	13.3 (-0.4 to 27.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: pCR rate in breast after 12 weeks of therapy with single agent LCL161 and LCL161 + paclitaxel, regardless of gene signature status (EAS1)

End point title	pCR rate in breast after 12 weeks of therapy with single agent LCL161 and LCL161 + paclitaxel, regardless of gene signature status (EAS1)

End point description:

To assess whether adding LCL161 to weekly paclitaxel enhances the efficacy of paclitaxel in women with triple negative breast cancer regardless of tumor gene expression signature status. This comparison is between the 2 study treatments, regardless of gene signature status. The measure median was used as these values are medians of posterior distribution of pCR rate for each treatment group. 95% Confidence interval is actually 95% credible interval.

End point type	Secondary

End point timeframe:

12 weeks

End point values	EAS1: LCL161 + Paclitaxel	EAS1: Paclitaxel only		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	105	102		
Units: Percentage of Participants				
median (confidence interval 95%)	15.5 (9.6 to 22.8)	15.7 (9.8 to 23.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: pCR rate in breast, regional nodes and axilla (EAS1)

End point title	pCR rate in breast, regional nodes and axilla (EAS1)

End point description:

To assess other indicators of disease response for the LCL161 + paclitaxel combination compared to paclitaxel alone. The pCR in breast, regional nodes, and axilla were determined based on the America Joint Committee on Cancer Staging [AJCC] stages T1c, T2, N0-N2, M0) were (AJCC) pathologic staging recorded on the eCRF: a patient was considered to be a responder in breast, regional nodes, and axilla if the pathological complete response was reported for breast and if the regional lymph nodes staging was pN0 (including i-, mol-, mol+). The measure median was used as these values are medians of posterior distribution of pCR rate for each group based on a Bayesian model. 95% Confidence interval is actually 95% credible interval.

End point type	Secondary

End point timeframe:

12 weeks

End point values	EAS1: LCL161 + Paclitaxel (gene expression signature positive)	EAS1: Paclitaxel only (gene expression signature positive)	EAS1: Paclitaxel only (gene expression signature negative)	EAS1: LCL161 + Paclitaxel (gene expression signature negative)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51	55
Units: Percentage of Participants				
median (confidence interval 95%)	21.5 (11.8 to 34)	19.1 (10 to 31.2)	5.5 (1.5 to 13.9)	6.9 (2.2 to 15.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Rates of breast conserving surgery and mastectomy - assessed by percentage of patients who underwent breast conserving surgery, masectomy and no surgery (EAS1)

End point title	Rates of breast conserving surgery and mastectomy - assessed by percentage of patients who underwent breast conserving surgery, masectomy and no surgery (EAS1)

End point description:

To assess other indicators of disease response for the LCL161 + paclitaxel combination compared to paclitaxel alone. Rates of breast conserving surgery and mastectomy also contributed to the overall assessment of disease response and were summarized by treatment arm within each gene expression signature status. For this analysis, patients with multicentric breast cancer were excluded, as all patients in this group were expected to be treated with mastectomy.

End point type	Secondary

End point timeframe:

16 weeks

End point values	EAS1: LCL161 + Paclitaxel (gene expression signature positive)	EAS1: Paclitaxel only (gene expression signature positive)	EAS1: LCL161 + Paclitaxel (gene expression signature negative)	EAS1: Paclitaxel only (gene expression signature negative)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48	45	51	47
Units: Percentage of participants				
number (not applicable)				
Breast Conserving Surgery	60.4	60	49	44.7
Mastectomy	25	26.7	23.5	29.8
No Surgery	14.6	13.3	27.5	25.5

Statistical analyses

No statistical analyses for this end point

Secondary: Caspase 3 activation in tumor by immunohistochemistry (IHC) - EAS1

End point title	Caspase 3 activation in tumor by immunohistochemistry (IHC) - EAS1

End point description:

To evaluate whether combination treatment with LCL161 and paclitaxel is associated with increased apoptosis compared to weekly paclitaxel alone. To evaluate whether combination treatment with LCL161 and paclitaxel was associated with increased apoptosis compared to weekly paclitaxel alone, cleaved caspase 3 activation in tumor by IHC was examined. Gene expression signature status is derived based on continuous gene expression signature score using cut-off 0.6661 (positive: score ≥ 0.6661; negative: score <0.6661); cycle = 28 days; each patient had either C1D2 or C1D9

End point type	Secondary

End point timeframe:

Baseline, Post-baeline at Cycle 1, Day 2 (C1D2) or Cycle 1, Day 9 (C1D9)

End point values	EAS1: LCL161 + Paclitaxel (gene expression signature negative)	EAS1: LCL161 + Paclitaxel (gene expression signature positive)	EAS1: Paclitaxel only (gene expression signature positive)	EAS1: Paclitaxel only (gene expression signature negative)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	50	51	51
Units: % of positive tumor cells				
arithmetic mean (standard deviation)				
EAS1-Baseline (n: 20, 16, 21, 22)	1.4 (± 3.3)	1.5 (± 1.6)	1.4 (± 1.3)	2.1 (± 2.8)
EAS1 Post-Baseline (n: 20, 16, 21, 22)	3.1 (± 3.1)	2.6 (± 1.4)	2.4 (± 1.7)	3.1 (± 6.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Caspase 3 activation in tumor by immunohistochemistry (IHC) - EAS2

End point title	Caspase 3 activation in tumor by immunohistochemistry (IHC) - EAS2

End point description:

To evaluate whether combination treatment with LCL161 and paclitaxel is associated with increased apoptosis compared to weekly paclitaxel alone. To evaluate whether combination treatment with LCL161 and paclitaxel was associated with increased apoptosis compared to weekly paclitaxel alone, cleaved caspase 3 activation in tumor by IHC was examined. Cycle = 28 days; each patient had either C1D2 or C1D9

End point type	Secondary

End point timeframe:

Baseline, Post-baeline at Cycle 1, Day 2 or Cycle 1, Day 9

End point values	EAS2: LCL161 + Paclitaxel (gene expression signature positive)	EAS2: Paclitaxel only (gene expression signature positive)	EAS2: LCL161 + Paclitaxel (gene expression signature negative)	EAS2: Paclitaxel only (gene expression signature negative)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	29	71	73
Units: % of positive tumor cells				
arithmetic mean (standard deviation)				
EAS2-Baseline (n: 13, 11, 28, 27)	1.3 (± 1.8)	1.6 (± 1.4)	1.5 (± 2.9)	1.9 (± 2.6)
EAS2 Post-Baseline (n:13, 11, 28, 27)	2.3 (± 1.4)	2.7 (± 1.9)	3.2 (± 2.7)	2.9 (± 5.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameters of LCL161 only for Cmax

End point title	Pharmacokinetics (PK) parameters of LCL161 only for Cmax

End point description:

To evaluate the PK of LCL161 when given in combination with paclitaxel.

End point type	Secondary

End point timeframe:

cycle 1 day 1, cycle 4 day 15

End point values	PAS: LCL161 + Paclitaxel (gene expression signature negative)			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: ng/mL				
median (full range (min-max))				
Cycle 1 Day 1 (n:97)	2230 (186 to 4740)			
Cycle 4 Day 15 (n:47)	2310 (491 to 5250)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameters of LCL161 only for Tmax

End point title	Pharmacokinetics (PK) parameters of LCL161 only for Tmax

End point description:

To evaluate the PK of LCL161 when given in combination with paclitaxel. The pharmacokinetic analysis set (PAS) consisted of all patients who had at least one blood sample providing evaluable PK data for LCL161.

End point type	Secondary

End point timeframe:

cycle 1 day 1, cycle 4 day 15

End point values	PAS: LCL161			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: hours				
median (full range (min-max))				
Cycle 1 Day 1 (n:97)	3.72 (0.5 to 5.8)			
Cycle 4 Day 15 (n:47)	3.5 (1 to 4.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameters of LCL161 only for AUClast

End point title	Pharmacokinetics (PK) parameters of LCL161 only for AUClast

End point description:

To evaluate the PK of LCL161 when given in combination with paclitaxel

End point type	Secondary

End point timeframe:

cycle 1 day 1, cycle 4 day 15

End point values	PAS: LCL161			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: ng*hr/mL				
median (full range (min-max))				
Cycle 1 Day 1 (n:97)	5250.7 (465.8 to 13379)			
Cycle 4 Day 15 (n:47)	5522.58 (1070.8 to 13745.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	LCL161 + paclitaxel

Reporting group description:

LCL161 + paclitaxel

Reporting group title	Paclitaxel

Reporting group description:

Paclitaxel

Serious adverse events	LCL161 + paclitaxel	Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 106 (42.45%)	7 / 103 (6.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	2 / 106 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	2 / 106 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEELING COLD			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA LIKE ILLNESS			

subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	19 / 106 (17.92%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	16 / 25	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	1 / 106 (0.94%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAPHYLACTIC SHOCK			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOKINE RELEASE SYNDROME			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG HYPERSENSITIVITY			
subjects affected / exposed	2 / 106 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERSENSITIVITY			
subjects affected / exposed	3 / 106 (2.83%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
IMMOBILE			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
COUGH			
subjects affected / exposed	1 / 106 (0.94%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	10 / 106 (9.43%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	10 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 106 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			

subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
SINUS TACHYCARDIA			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			

subjects affected / exposed	1 / 106 (0.94%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISSEMINATED INTRAVASCULAR COAGULATION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 106 (0.94%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPH NODE PAIN			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	2 / 106 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	2 / 106 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

DERMATITIS			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	2 / 106 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
POLYARTHRITIS			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ATYPICAL PNEUMONIA			
subjects affected / exposed	3 / 106 (2.83%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE INFECTION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			

subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	4 / 106 (3.77%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	4 / 106 (3.77%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

HYPONATRAEMIA			
subjects affected / exposed	2 / 106 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	LCL161 + paclitaxel	Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 106 (100.00%)	101 / 103 (98.06%)	
Vascular disorders			
FLUSHING			
subjects affected / exposed	6 / 106 (5.66%)	7 / 103 (6.80%)	
occurrences (all)	8	9	
HOT FLUSH			
subjects affected / exposed	17 / 106 (16.04%)	15 / 103 (14.56%)	
occurrences (all)	23	17	
HYPERTENSION			
subjects affected / exposed	3 / 106 (2.83%)	6 / 103 (5.83%)	
occurrences (all)	3	8	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	16 / 106 (15.09%)	11 / 103 (10.68%)	
occurrences (all)	27	15	
CHILLS			
subjects affected / exposed	12 / 106 (11.32%)	4 / 103 (3.88%)	
occurrences (all)	14	5	
FATIGUE			
subjects affected / exposed	48 / 106 (45.28%)	38 / 103 (36.89%)	
occurrences (all)	62	40	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	6 / 106 (5.66%)	0 / 103 (0.00%)	
occurrences (all)	8	0	
OEDEMA PERIPHERAL			

subjects affected / exposed	12 / 106 (11.32%)	3 / 103 (2.91%)	
occurrences (all)	15	5	
PYREXIA			
subjects affected / exposed	44 / 106 (41.51%)	9 / 103 (8.74%)	
occurrences (all)	67	10	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	8 / 106 (7.55%)	1 / 103 (0.97%)	
occurrences (all)	8	1	
HYPERSENSITIVITY			
subjects affected / exposed	7 / 106 (6.60%)	6 / 103 (5.83%)	
occurrences (all)	11	7	
Reproductive system and breast disorders			
BREAST PAIN			
subjects affected / exposed	9 / 106 (8.49%)	10 / 103 (9.71%)	
occurrences (all)	11	10	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	30 / 106 (28.30%)	10 / 103 (9.71%)	
occurrences (all)	33	11	
DYSPNOEA			
subjects affected / exposed	24 / 106 (22.64%)	7 / 103 (6.80%)	
occurrences (all)	28	7	
EPISTAXIS			
subjects affected / exposed	15 / 106 (14.15%)	9 / 103 (8.74%)	
occurrences (all)	16	9	
OROPHARYNGEAL PAIN			
subjects affected / exposed	16 / 106 (15.09%)	4 / 103 (3.88%)	
occurrences (all)	16	7	
PNEUMONITIS			
subjects affected / exposed	6 / 106 (5.66%)	0 / 103 (0.00%)	
occurrences (all)	6	0	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	8 / 106 (7.55%)	8 / 103 (7.77%)	
occurrences (all)	8	8	

INSOMNIA			
subjects affected / exposed	22 / 106 (20.75%)	17 / 103 (16.50%)	
occurrences (all)	26	25	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	15 / 106 (14.15%)	11 / 103 (10.68%)	
occurrences (all)	18	12	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	13 / 106 (12.26%)	8 / 103 (7.77%)	
occurrences (all)	16	11	
HAEMOGLOBIN DECREASED			
subjects affected / exposed	8 / 106 (7.55%)	3 / 103 (2.91%)	
occurrences (all)	12	3	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	10 / 106 (9.43%)	2 / 103 (1.94%)	
occurrences (all)	14	4	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	8 / 106 (7.55%)	3 / 103 (2.91%)	
occurrences (all)	13	3	
Injury, poisoning and procedural complications			
PROCEDURAL PAIN			
subjects affected / exposed	7 / 106 (6.60%)	9 / 103 (8.74%)	
occurrences (all)	7	9	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	12 / 106 (11.32%)	7 / 103 (6.80%)	
occurrences (all)	17	7	
DYSGEUSIA			
subjects affected / exposed	24 / 106 (22.64%)	9 / 103 (8.74%)	
occurrences (all)	32	9	
HEADACHE			
subjects affected / exposed	35 / 106 (33.02%)	18 / 103 (17.48%)	
occurrences (all)	48	29	
HYPOAESTHESIA			

subjects affected / exposed	2 / 106 (1.89%)	6 / 103 (5.83%)	
occurrences (all)	3	7	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	13 / 106 (12.26%)	28 / 103 (27.18%)	
occurrences (all)	14	34	
NEUROTOXICITY			
subjects affected / exposed	11 / 106 (10.38%)	10 / 103 (9.71%)	
occurrences (all)	15	12	
PARAESTHESIA			
subjects affected / exposed	9 / 106 (8.49%)	4 / 103 (3.88%)	
occurrences (all)	10	9	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	25 / 106 (23.58%)	17 / 103 (16.50%)	
occurrences (all)	30	19	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	27 / 106 (25.47%)	13 / 103 (12.62%)	
occurrences (all)	32	15	
NEUTROPENIA			
subjects affected / exposed	33 / 106 (31.13%)	9 / 103 (8.74%)	
occurrences (all)	58	15	
Eye disorders			
VISION BLURRED			
subjects affected / exposed	7 / 106 (6.60%)	1 / 103 (0.97%)	
occurrences (all)	7	1	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	11 / 106 (10.38%)	8 / 103 (7.77%)	
occurrences (all)	13	9	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	7 / 106 (6.60%)	4 / 103 (3.88%)	
occurrences (all)	12	4	
CONSTIPATION			
subjects affected / exposed	24 / 106 (22.64%)	24 / 103 (23.30%)	
occurrences (all)	28	24	
DIARRHOEA			

subjects affected / exposed	76 / 106 (71.70%)	23 / 103 (22.33%)	
occurrences (all)	160	35	
DRY MOUTH			
subjects affected / exposed	10 / 106 (9.43%)	3 / 103 (2.91%)	
occurrences (all)	11	5	
DYSPEPSIA			
subjects affected / exposed	12 / 106 (11.32%)	10 / 103 (9.71%)	
occurrences (all)	15	10	
NAUSEA			
subjects affected / exposed	45 / 106 (42.45%)	32 / 103 (31.07%)	
occurrences (all)	70	41	
STOMATITIS			
subjects affected / exposed	26 / 106 (24.53%)	18 / 103 (17.48%)	
occurrences (all)	32	20	
VOMITING			
subjects affected / exposed	21 / 106 (19.81%)	16 / 103 (15.53%)	
occurrences (all)	33	19	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	72 / 106 (67.92%)	69 / 103 (66.99%)	
occurrences (all)	72	70	
ERYTHEMA			
subjects affected / exposed	10 / 106 (9.43%)	8 / 103 (7.77%)	
occurrences (all)	13	13	
NAIL DISORDER			
subjects affected / exposed	5 / 106 (4.72%)	6 / 103 (5.83%)	
occurrences (all)	5	6	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	8 / 106 (7.55%)	3 / 103 (2.91%)	
occurrences (all)	8	3	
PRURITUS			
subjects affected / exposed	28 / 106 (26.42%)	9 / 103 (8.74%)	
occurrences (all)	37	11	
RASH			

subjects affected / exposed	44 / 106 (41.51%)	27 / 103 (26.21%)	
occurrences (all)	55	33	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	21 / 106 (19.81%)	15 / 103 (14.56%)	
occurrences (all)	25	18	
BACK PAIN			
subjects affected / exposed	10 / 106 (9.43%)	8 / 103 (7.77%)	
occurrences (all)	12	8	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	11 / 106 (10.38%)	6 / 103 (5.83%)	
occurrences (all)	16	7	
MYALGIA			
subjects affected / exposed	23 / 106 (21.70%)	18 / 103 (17.48%)	
occurrences (all)	83	51	
PAIN IN EXTREMITY			
subjects affected / exposed	11 / 106 (10.38%)	6 / 103 (5.83%)	
occurrences (all)	12	8	
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	10 / 106 (9.43%)	3 / 103 (2.91%)	
occurrences (all)	13	3	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	12 / 106 (11.32%)	5 / 103 (4.85%)	
occurrences (all)	13	5	
HYPERGLYCAEMIA			
subjects affected / exposed	6 / 106 (5.66%)	8 / 103 (7.77%)	
occurrences (all)	6	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2012	The primary purpose of this amendment was to evaluate the performance of the gene expression signature as a means of identifying patients more likely to respond to treatment with paclitaxel and LCL161. This amendment expanded the size of the study to incorporate patients with gene expression signature positive and negative disease, and compared the response to treatment in these two populations.
29 January 2013	Two changes have been made to satisfy local regulatory requirements in Ireland. All patients in the experimental treatment arm were to receive dexamethasone as a premedication for paclitaxel + LCL161. In addition, for patients who were scheduled to undergo surgery, recovery from chemotherapy included laboratory evidence of hematological recovery.
16 December 2013	This amendment resulted in three changes to the protocol. In addition to the planned analysis for futility in the gene expression signature positive group, an interim futility analysis was also now to be done separately for patients in the signature negative group. To maximize the efficiency of the data collection and analysis, this was to be done when the interim analysis was performed for the positive group (approximately 50 patients in the positive group). In response to requests from trial Investigators, inclusion criterion #5 was changed to allow the treatment of patients with Stage T1c disease by AJCC criteria. Compared with other breast cancer subtypes triple negative breast cancer has a higher risk of visceral metastasis, and patients with T1c disease often receive chemotherapy in the neoadjuvant setting where response to treatment can be assessed. Also, alternative methods of assessment for HER2/ErbB2 are also now allowed, a change to inclusion criterion #2.
01 April 2014	Under Amendment 3, eligibility was expanded to include patients with T1c, N0-2, M0 disease. A recent health authority reviewing Amendment 3 requested that patients with T1c disease not be enrolled unless the response to treatment is found to be acceptably high after reviewing the results of the pending interim analysis. Based on the feedback from a Health Authority, Novartis decided to modify the Inclusion criterion #5 to restrict enrollment to patients with AJCC T2, N0-2, M0 disease. As per the health authority, this change could be reconsidered after review of the interim analysis data. If so, an appropriate amendment was to be filed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: