



## 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.nov> for 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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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                                     |
| <b>Arm title</b>             | Paclitaxel with LCL161 (Positive group) |

Arm description:

Patients who were gene signature positive were randomized to the experimental arm received paclitaxel 80 mg/m<sup>2</sup> 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/m<sup>2</sup> weekly and was administered as infusion.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Paclitaxel without LCL161 (Positive group) |
|------------------|--|

Arm description:

Patients who were gene signature positive were randomized to the control arm received paclitaxel 80 mg/m<sup>2</sup> 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/m<sup>2</sup> weekly and was administered as infusion.

|  |  |
|--|--|
| <b>Arm title</b>   | Paclitaxel with LCL161 (Negative group)    |
| Arm description:<br>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:<br>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:<br>Paclitaxel was given as 80 mg/m2 weekly and was administered as infusion.  |  |
| <b>Arm title</b>   | Paclitaxel without LCL161 (Negative group) |

|  |                   |
|--|-------------------|
| Arm description:<br>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:<br>Paclitaxel was given as 80 mg/m2 weekly and was administered as infusion.                                    |                   |

| <b>Number of subjects in period 1</b> | 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                                       |

| <b>Number of subjects in period 1</b> | 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:<br>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:<br>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:<br>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:<br>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<br>Units: Participants     |   |  |   |
| < 65 years                                 | 46                                      | 46   | 52                                      |
| >= 65 years                                | 5                                       | 4  | 3                                       |
| Age Continuous<br>Units: Years             |   |  |   |
| arithmetic mean                            | 49.4                                    | 48.4                                       | 47.8                                    |
| standard deviation                         | ± 9.83                                  | ± 11.08                                    | ± 10.46                                 |
| Gender, Male/Female<br>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<br>Units: Participants     |  |       |  |
| < 65 years                                 | 50   | 194   |  |
| >= 65 years                                | 3  | 15    |  |
| Age Continuous<br>Units: Years             |  |       |  |
| arithmetic mean                            | 49   | -     |  |
| standard deviation                         | ± 8.92                                     |       |  |
| Gender, Male/Female<br>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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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 (CrI) 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

| <b>End point values</b>           | 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[1]</sup> |
|-----------------|---|

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 <sup>[2]</sup> |
| 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

|                                  |                           |  |  |  |
|----------------------------------|---------------------------|--|--|--|
| <b>End point values</b>          | 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

|                                  |                       |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>          | 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  $\geq$  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-baseline 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 ( $\pm$ 3.3)   | 1.5 ( $\pm$ 1.6)   | 1.4 ( $\pm$ 1.3)   | 2.1 ( $\pm$ 2.8)   |
| EAS1 Post-Baseline (n: 20, 16, 21, 22) | 3.1 ( $\pm$ 3.1)   | 2.6 ( $\pm$ 1.4)   | 2.4 ( $\pm$ 1.7)   | 3.1 ( $\pm$ 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-baseline 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           |  |
| DYSпноEA  |                  |                 |  |
| 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 JIROVECI 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 %

| <b>Non-serious adverse events</b>                     | 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                                     |                     |                    |  |

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

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| INSOMNIA<br>subjects affected / exposed<br>occurrences (all)   | 22 / 106 (20.75%)<br>26 | 17 / 103 (16.50%)<br>25 |  |
| Investigations<br>ALANINE AMINOTRANSFERASE<br>INCREASED<br>subjects affected / exposed<br>occurrences (all)              | 15 / 106 (14.15%)<br>18 | 11 / 103 (10.68%)<br>12 |  |
| ASPARTATE AMINOTRANSFERASE<br>INCREASED<br>subjects affected / exposed<br>occurrences (all)                              | 13 / 106 (12.26%)<br>16 | 8 / 103 (7.77%)<br>11   |  |
| HAEMOGLOBIN DECREASED<br>subjects affected / exposed<br>occurrences (all)  | 8 / 106 (7.55%)<br>12   | 3 / 103 (2.91%)<br>3    |  |
| NEUTROPHIL COUNT DECREASED<br>subjects affected / exposed<br>occurrences (all)   | 10 / 106 (9.43%)<br>14  | 2 / 103 (1.94%)<br>4    |  |
| WHITE BLOOD CELL COUNT<br>DECREASED<br>subjects affected / exposed<br>occurrences (all)                                  | 8 / 106 (7.55%)<br>13   | 3 / 103 (2.91%)<br>3    |  |
| Injury, poisoning and procedural<br>complications<br>PROCEDURAL PAIN<br>subjects affected / exposed<br>occurrences (all) | 7 / 106 (6.60%)<br>7    | 9 / 103 (8.74%)<br>9    |  |
| Nervous system disorders<br>DIZZINESS<br>subjects affected / exposed<br>occurrences (all)                                | 12 / 106 (11.32%)<br>17 | 7 / 103 (6.80%)<br>7    |  |
| DYSGEUSIA<br>subjects affected / exposed<br>occurrences (all)  | 24 / 106 (22.64%)<br>32 | 9 / 103 (8.74%)<br>9    |  |
| HEADACHE<br>subjects affected / exposed<br>occurrences (all)   | 35 / 106 (33.02%)<br>48 | 18 / 103 (17.48%)<br>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<br>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<br>occurrences (all) | 44 / 106 (41.51%)<br>55 | 27 / 103 (26.21%)<br>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> for complete trial results.

Notes: