Clinical trial results:
Randomized, open-label, phase II study comparing the efficacy and safety of cabazitaxel versus weekly paclitaxel given as neo-adjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer.

Summary

EudraCT number	2012-003330-16
Trial protocol	DE
Global end of trial date	27 August 2015

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022
Summary attachment (see zip file)	CSR Synopsis (CSR Synopsis Genevieve V 1.0.pdf)

Trial information

Trial identification

Sponsor protocol code	GBG74

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01779479
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Martin-Behaim-Str. 12, Neu-Isenburg, Germany, 63263
Public contact	Medicine and Research, GBG Forschungs GmbH, 49 610274800, publications@gbg.de
Scientific contact	Medicine and Research, GBG Forschungs GmbH, 49 610274800, publications@gbg.de

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	30 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the pathologic complete response (pCR) rate in the breast (ypT0/is ypN0/+) in patients with operable Triple Negative or luminal B/HER2 normal breast cancer treated with either cabazitaxel or weekly paclitaxel.

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving.

Background therapy: -

Evidence for comparator:

Cabazitaxel is compared against weekly paclitaxel which is currently most widely used treatment of breast cancer patients. A head-to-head comparison in the neoadjuvant setting will allow a rapid and precise comparison of efficacy and tolerability of cabacitaxel versus paclitaxel to decide in how far further development of this taxoid in breast cancer is reasonable.

Actual start date of recruitment	01 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 333
Worldwide total number of subjects	333
EEA total number of subjects	333

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	281
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between April 2013 and June 2015, 407 patients were screened, 333 were randomised (166 in cabazitaxel arm and 167 in paclitaxel arm) and started treatment of whom 263 (74.7% in cabazitaxel arm and 83.2% in paclitaxel arm) completed treatment.

Pre-assignment

Screening details:

Eligibility criteria were primary invasive BC, clinical stage cT2-3 any cN or cT1c cN+/pN(SLN+) and centrally confirmed prior to enrolment TNBC or luminal B/HER2-negative BC.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cabazitaxel

Arm description:

A total of 166 patients were randomised to receive cabazitaxel and started treatment, 124 patients completed treatment regularly. After amendment 2, 78 patients without pCR received additional anthracycline-containing chemotherapy prior surgery. Overall, 83 patients received surgery after cabazitaxel treatment and 78 underwent surgery after additional anthracycline-containing chemotherapy. Note, the number of patients started treatment is given for "started".

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	
Other name	Jevtana, EU/1/11/676/001
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Cabazitaxel 25 mg/m² i.v. (Day 1) every 3 weeks (cycle) as 1-hour i.v infusion for a total of up to 4 cycles over a maximum total treatment period of 15 weeks before surgery.

Arm title	Paclitaxel

Arm description:

A total of 167 patients were randomised to receive paclitaxel and started treatment, 139 patients completed treatment regularly. After amendment 2, 77 patients without pCR received additional anthracycline-containing chemotherapy prior surgery. Overall, 88 patients received surgery after paclitaxel treatment and 75 underwent surgery after additional anthracycline-containing chemotherapy . Note, the number of patients started treatment is given for "started".

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	77226.00.00
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Paclitaxel 80 mg/m² as 1-hour i.v infusion. Patients will receive weekly (Day 1, 8, 15) paclitaxel administrations for a maximum of 12 infusions for a maximum of 4 cycles over a maximum total treatment period of 15 weeks before surgery (1 cycle = 3 weeks).
Paclitaxel is used according to the recommendations of the manufacturers via normal procedures at

each site.

Number of subjects in period 1	Cabazitaxel	Paclitaxel
Started	166	167
Completed	124	139
Not completed	42	28
Adverse event, serious fatal	2	-
Physician decision	6	6
progression	20	11
Adverse event, non-fatal	13	7
patient's decision	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Cabazitaxel

Reporting group description:

A total of 166 patients were randomised to receive cabazitaxel and started treatment, 124 patients completed treatment regularly. After amendment 2, 78 patients without pCR received additional anthracycline-containing chemotherapy prior surgery. Overall, 83 patients received surgery after cabazitaxel treatment and 78 underwent surgery after additional anthracycline-containing chemotherapy. Note, the number of patients started treatment is given for "started".

Reporting group title	Paclitaxel

Reporting group description:

A total of 167 patients were randomised to receive paclitaxel and started treatment, 139 patients completed treatment regularly. After amendment 2, 77 patients without pCR received additional anthracycline-containing chemotherapy prior surgery. Overall, 88 patients received surgery after paclitaxel treatment and 75 underwent surgery after additional anthracycline-containing chemotherapy . Note, the number of patients started treatment is given for "started".

Reporting group values	Cabazitaxel	Paclitaxel	Total
Number of subjects	166	167	333
Age categorical Units: Subjects			
Adults (18-64 years)	145	136	281
From 65-84 years	21	31	52
Gender categorical Units: Subjects			
Female	166	167	333
Male	0	0	0

End points

End points reporting groups

Reporting group title	Cabazitaxel

Reporting group description:

A total of 166 patients were randomised to receive cabazitaxel and started treatment, 124 patients completed treatment regularly. After amendment 2, 78 patients without pCR received additional anthracycline-containing chemotherapy prior surgery. Overall, 83 patients received surgery after cabazitaxel treatment and 78 underwent surgery after additional anthracycline-containing chemotherapy. Note, the number of patients started treatment is given for "started".

Reporting group title	Paclitaxel

Reporting group description:

A total of 167 patients were randomised to receive paclitaxel and started treatment, 139 patients completed treatment regularly. After amendment 2, 77 patients without pCR received additional anthracycline-containing chemotherapy prior surgery. Overall, 88 patients received surgery after paclitaxel treatment and 75 underwent surgery after additional anthracycline-containing chemotherapy . Note, the number of patients started treatment is given for "started".

Primary: pCR (ypT0/is ypN0/+)

End point title	pCR (ypT0/is ypN0/+)

End point description:

The primary endpoint pCR (ypT0/is ypN0/+) was analysed in the mITT analysis set. The pCR rate was defined as the complete absence of invasive carcinoma on histological examination in the breast irrespective of lymph node involvement (ypT0/Tis, ypN0/+) at the time of definitive surgery and confirmed by independent blinded centralized histology report review. With Amendment 2 patients with invasive tumor residuals after end of study treatment had the option to receive anthracycline-containing chemotherapy prior to surgery. This change resulted in a modification of the definition of treatment failures for the primary endpoint: patients in whom pCR could not be determined (e.g. patients in whom histology was not evaluable) or who have invasive tumor residuals in the core biopsy taken after end of study treatment was included in the denominator, i.e. these patients was considered as treatment failures.

End point type	Primary

End point timeframe:

from treatment start until surgery after study treatment; the entire treatment period was 12 weeks

End point values	Cabazitaxel	Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	167		
Units: percent				
number (confidence interval 95%)				
pCR (ypT0/is ypN0/+)	1.2 (0.0 to 2.9)	10.8 (6.1 to 15.5)		

Statistical analyses

Statistical analysis title	pCR (ypT0/is ypN0/+) - rates

Statistical analysis description:

In the primary efficacy analysis the difference of the pCR rates was tested using a one-sided Fisher’s exact test with a type I error of 10%.

Comparison groups	Cabazitaxel v Paclitaxel
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.001
Method	Fisher exact

Notes:

[1] - The pCR rates for each treatment group and the difference in pCR rates between treatment arms with their 95% CIs were calculated according to Pearson and Clopper

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the study treatment period were reported.

Adverse event reporting additional description:

Predefined AEs are reported per patient during the complete treatment duration for the safety population (N=133). Non-serious AEs any grade per patient occurring more frequently (> 20%) are presented. Of note, overall number of single AE occurrences per term was not assessed, only per patient; SAEs are reported regardless of causality.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	n.a.

Reporting groups

Reporting group title	Cabazitaxel

Reporting group description:

Cabazitaxel given as neo-adjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer

Reporting group title	Paclitaxel

Reporting group description:

Paclitaxel was given as neo-adjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer.

Serious adverse events	Cabazitaxel	Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 166 (25.30%)	17 / 167 (10.18%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms			
subjects affected / exposed	0 / 166 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	0 / 166 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Other vascular disorders			
subjects affected / exposed	1 / 166 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Other neurological disorders			
subjects affected / exposed	2 / 166 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 166 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 166 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	23 / 166 (13.86%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 23	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	17 / 166 (10.24%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 17	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 166 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever without neutropenia			

subjects affected / exposed	2 / 166 (1.20%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain NOS			
subjects affected / exposed	0 / 166 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other general disorders and administration site conditions			
subjects affected / exposed	2 / 166 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Immune system disorders			
Allergic reactions			
subjects affected / exposed	1 / 166 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 166 (0.60%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	5 / 166 (3.01%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis/esophagitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Other gastrointestinal disorders			
subjects affected / exposed	2 / 166 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 166 (0.60%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Other renal and urinary disorders			
subjects affected / exposed	6 / 166 (3.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	6 / 166 (3.61%)	8 / 167 (4.79%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cabazitaxel	Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	166 / 166 (100.00%)	167 / 167 (100.00%)	
Investigations			
Alkaline phosphatase increased			
subjects affected / exposed	34 / 166 (20.48%)	14 / 167 (8.38%)	
occurrences (all)	34	14	
Aspartate aminotransferase			

increased			
subjects affected / exposed	38 / 166 (22.89%)	43 / 167 (25.75%)	
occurrences (all)	38	43	
Alanine aminotransferase increased			
subjects affected / exposed	66 / 166 (39.76%)	75 / 167 (44.91%)	
occurrences (all)	66	75	
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 166 (18.07%)	38 / 167 (22.75%)	
occurrences (all)	30	38	
Peripheral sensory neuropathy			
subjects affected / exposed	35 / 166 (21.08%)	105 / 167 (62.87%)	
occurrences (all)	35	105	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	135 / 166 (81.33%)	122 / 167 (73.05%)	
occurrences (all)	135	122	
Leukopenia			
subjects affected / exposed	133 / 166 (80.12%)	97 / 167 (58.08%)	
occurrences (all)	133	97	
Neutropenia			
subjects affected / exposed	121 / 166 (72.89%)	62 / 167 (37.13%)	
occurrences (all)	121	62	
Lymphopenia			
subjects affected / exposed	84 / 166 (50.60%)	54 / 167 (32.34%)	
occurrences (all)	84	54	
Thrombopenia			
subjects affected / exposed	60 / 166 (36.14%)	13 / 167 (7.78%)	
occurrences (all)	60	13	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	112 / 166 (67.47%)	118 / 167 (70.66%)	
occurrences (all)	112	118	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	77 / 166 (46.39%)	48 / 167 (28.74%)	
occurrences (all)	77	48	
Diarrhea			
subjects affected / exposed	73 / 166 (43.98%)	40 / 167 (23.95%)	
occurrences (all)	73	40	
Mucositis/esophagitis			
subjects affected / exposed	38 / 166 (22.89%)	60 / 167 (35.93%)	
occurrences (all)	38	60	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	5 / 166 (3.01%)	42 / 167 (25.15%)	
occurrences (all)	5	42	
Dyspnea			
subjects affected / exposed	25 / 166 (15.06%)	37 / 167 (22.16%)	
occurrences (all)	25	37	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	96 / 166 (57.83%)	150 / 167 (89.82%)	
occurrences (all)	96	150	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	53 / 166 (31.93%)	50 / 167 (29.94%)	
occurrences (all)	53	50	
Myalgia			
subjects affected / exposed	28 / 166 (16.87%)	35 / 167 (20.96%)	
occurrences (all)	28	35	
Infections and infestations			
Infection			
subjects affected / exposed	50 / 166 (30.12%)	42 / 167 (25.15%)	
occurrences (all)	50	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2013	Additional precaution regarding application of IMP cabazitaxel with OATP1B1 substrates
20 December 2013	With Amendment 2 the study design was changed to give patients with invasive tumor residuals after end of study treatment detected in core biopsy the option to receive anthracycline-containing chemotherapy prior to surgery. This change resulted in a modification of the definition of treatment failures for the primary endpoint: patients in whom success cannot be determined (e.g. patients in whom histology is not evaluable) or who have invasive tumor residuals in the core biopsy taken after end of study treatment will be included in the denominator, i.e. these patients will be considered as treatment failures.
28 November 2014	Prolongation of enrolment period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28768217