CLINICAL STUDY REPORT

Randomized, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neo-adjuvant treatment in patients with operable Triple Negative or luminal B/HER2 normal Breast Cancer (GENEVIEVE)

Eudract No: 2012-003330-16

Investigational Products:	**Cabazitaxel/Paclitaxel**
Indication:	**Breast Cancer**
Study Protocol:	**GBG74 Am. 3 Version 7/06-Nov-2014**
Phase:	**II**
Report Version / Number:	**Final 1.0**

First Patient Enrolled: March 11, 2013
Last Patient Completed: August 27, 2015

Coordinating Investigator (according to the German drug law AMG):
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Sponsor
GBG Forschungs GmbH
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Date of this report:	April, 30th 2016
Date of any previous reports:	N/A

1.0 APPROVAL SIGNATURES

STUDY TITLE: Randomized, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neo-adjuvant treatment in patients with operable Triple Negative or luminal B/HER2 normal Breast Cancer (GENEVIEVE)

STUDY NUMBER: GBG74

I, the undersigned, have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

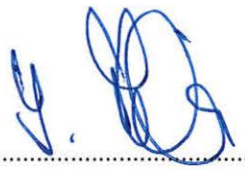
SIGNATURE: DATE:

24.05.16

Gunter von Minckwitz, Prof. Dr. med

Luisenkrankenhaus Düsseldorf

c/o GBG Forschungs GmbH



24.5.16

Sibylle Loibl, Prof. Dr. med.

Director of Medicine and Research

GBG Forschungs GmbH

Burchardi

31.05.2016

Nicole Burchardi, Dr.

Study Statistician

GBG Forschungs GmbH

2.0 SYNOPSIS

Name of Sponsor: GBG Forschungs GmbH	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of finished product: Cabazitaxel/Paclitaxel	Volume:	
Name of active ingredient: Cabazitaxel/Paclitaxel	Page:	

Title of Study:

Randomized, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neo-adjuvant treatment in patients with operable Triple Negative or luminal B/HER2 normal Breast Cancer (GENEVIEVE)

Coordinating Investigator:

Gunter von Minckwitz, Prof. Dr. med.

Luisenkrankenhaus Düsseldorf

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Study Center(s):

A total of 55 centers in one country (Germany) participated in this study.

Publication (reference):

Paepke S, Kümmel S, Blohmer JU, et al. Randomized, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neo-adjuvant treatment in patients with operable Triple Negative or luminal B/HER2 normal Breast Cancer (GENEVIEVE). J Clin Oncol 31, 2013 (suppl; abstr TPS1138)

Studied Period (years):

Date of the first patient enrolled: 11 March 2013

Date of the last patient completed: 27 August 2015

Phase of Development:

Phase II

Objectives:

Primary Objectives:

The primary objective of this study was 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.

Secondary Objectives:

The secondary objectives of this study is to assess:

pCR rates per arm separately for the stratified subpopulation

objective response rate (ORR) after end of study treatment in the breast according to WHO criteria

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pCR rate defined as ypT0 ypN0

pCR rate defined as ypT0/is ypN0

pCR rate in the axillary lymph nodes (ypN0) (only considering patients with immediate surgery after end of study treatment)

pCR rate of all patients irrespective of core biopsy result after end of study treatment

pCR rate and local recurrence free survival (LRFS) in patients with a clinical complete response (cCR) and a negative core biopsy before surgery

Breast conservation surgery rate (for all patients and separately for the following subgroups: patients with cCR, without invasive tumor residuals, and with invasive tumor residuals in the core biopsy)

The toxicity (NCI CTCAE V4.03) and compliance in both arms

Invasive loco-regional recurrence free survival (LRRFS), distant-disease-free survival (DDFS), invasive disease-free survival (IDFS), and overall survival (OS)

To explore the biomarkers and profiles potentially predicting response to treatment

Methodology:

This is a prospective multicenter, randomized, open-label, study comparing the efficacy and the safety of four 3-weekly cycles cabazitaxel versus 12-weekly paclitaxel given as neo-adjuvant treatment in patients with operable triple negative or luminal B/HER2-normal breast cancer. Randomization has been conducted by a 1:1 ratio.

Stratification factors for randomization have been:

Nodal stage status (cN0 vs. c(p)N+)

Subtype (TNBC vs. luminal B/HER2-normal)

In both study arms, treatment has been given until proof of having no pathological complete response by core biopsy, surgery, disease progression, unacceptable toxicity, or withdrawal of consent of the patient.

Number of patients (planned and analyzed):

planned: 332, enrolled: 403, randomized: 333, analyzed (safety): 333, analyzed (efficacy): 333

Diagnosis and Main Criteria for Inclusion:

Women with histologically confirmed carcinoma of the breast, treatment naïve, with lesions measurable preferably per sonography (≥1 cm) or clinically (≥2 cm). Patients must be in following stages:

cT3, cT2, cT1c and cN+, cT1c and pNSLN+

Triple negative or luminal B/HER2 subtype must be centrally confirmed prior to randomization.

Test Products, Dose and Mode of Administration, Batch Number:

Cabazitaxel 25mg/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.

Cabazotaxel is supplied as a sterile, non-pyrogenic non-aqueous yellowish to brownish-yellow solution contained in a 15mL clear glass vial, with a stopper crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap.

Single-dose vial, containing a total of 60mg of cabazitaxel expressed as anhydrous and solvent-free basis, per 1.5 mL solution.

The fill volume has been established to include an overfill [i.e., 1.5 mL (nominal volume) +0.33mL]

This overfill was determined to ensure that a 10mg/mL concentration is obtained in the premix and that 60mg dose can be extracted.

Solvent: The solvent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 13% w/w ratio of ethanol 95% in water for injection. This solution is contained in a 15mL clear glass vial, stoppered and crimped to the vial with either an aluminium cap covered with a light grey plastic flip-off cap or a gold-color aluminium cap covered with a plastic flip-off cap.

The solution is a clear colorless liquid.

Each vial is overfilled to ensure that a 10mg/mL concentration is obtained in the Premix and that 60mg dose can be extracted [i.e., 4.5 mL (nominal volume) + 1.17mL].

Each vial of cabazitaxel must be diluted with the entire content of one solvent vial.

Batch-Numbers: IP0003361, IP0003838, IP0004256.

Duration of Treatment:

Cabazitaxel: four 3-weekly-cycles

Reference Therapy, Dose and Mode of Administration, Batch Number:

Paclitaxel: 12 weekly

Criteria for Evaluation:

Efficacy:

Primary endpoint:

Efficacy analysis are performed in the overall cohort and repeated by subtype (TNBC and luminal B/HER2 normal) and nodal status.

The primary efficacy endpoint is the pCR rate 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.

It will be assessed using all removed breast and lymphatic tissues from all surgeries. Patients in whom success cannot be determined (e.g. patients in whom histology is not evaluable) or which have invasive tumor residuals in the core biopsy taken after end of study treatment will be included in the denominator, i.e. theses

patients will be considered treatment failures.

Secondary endpoints:

Short-term efficacy endpoints (ypT0 ypN0; ypT0/is ypN0 ypT(any) ypN0) and ypT0/is ypN0 rate, considered as explorative test, summarized as rates in each treatment group, irrespective of core biopsy result after end of study treatment.

Breast conservation rate defined as tumorectomy, segmentectomy or quadrantectomy.

Clinical (c) and imaging (i) response, assessed after the 2nd cycle and after end of study treatment by physical examination and imaging tests. Tumor response is defined as either a partial response (PR) or complete response (CR) according to WHO criteria. (CR) is defined as no evidence of disease in the breast using ultrasound and/or MRI, in exceptional cases mammography or physical examination. (PR) is defined as a reduction of the two largest perpendicular diameters o the primary tumor size by 50% or more; (PD=progressive disease) is defined as an increase by 25% or more or a new lesion. (NC=no change) is the remaining scenario.

LRRFS, RRFS, LRFS, DDFS, IDFS and OS are defined as the time period between registration and first event.

Safety:

Descriptive statistics for the 2 treatments on patients whose treatment had to be reduced, delayed or permanently stopped
Reason for termination includes aspect of efficacy (e.g. due to tumor progression), safety (e.g. due to adverse events) and compliance (e.g. due to withdrawal of consent)

Translational research:

Exploratory analysis to identify possible relationship between biomarkers and drug activity (short and log-term parameters as pCR, no treatment effect, RFS and OS).

Statistical Methods:

Sample size determination

Assuming a pCR rate in the breast of 15% in control arm (GBG database) and targeting a smallest clinical improvement of 10% (i.e. pCR rate = 25% in experimental arm), 163 patients per arm are required for the one-sided 10% proportion comparison test (one-sided type I error rate) to reach 80% power.

A total of 326 randomized and treated patients are hence targeted. Further assuming around 2% of patients randomized but not treated, one needs about 332 randomized patients.

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SUMMARY

Efficacy Results:

Between 4/2013 and 6/2015, a total of 333 patients have been randomized and started treatment with 74.7 and 83.2% of patients completing treatment in the cabazitaxel and paclitaxel arm, respectively. Among patients who discontinued taxane treatment due to progression, 50% in the cabazitaxel arm vs 55% in the paclitaxel arm had TNBC, and 50% vs 18% were cN0, respectively .. Baseline characteristics were well balanced,. pCR was lower in the cabazitaxel arm compared to the paclitaxel arm .

Safety Results:

A total of 48 (29%) patients in the cabazitaxel arm and 20 (12%) in the paclitaxel arm had at least one serious adverse event (SAE). Serious hematological and non-hematological toxicities occuring with cabazitaxel and paclitaxel have been summarized.

The median time of treatment exposure was 12 (range 3-15) weeks in the cabazitaxel arm corresponding to a median of 4 cycles (range 1-4) compared to 12 (1-17) weeks in the paclitaxel arm (p=0.019). The relative total dose intensity did not differ between the cabazitaxel and paclitaxel arm, with 100% (range 1.6-101.2) and 100% (8.3-102.4), respectively (p=0.822). There were significantly less treatment delays in the cabazitaxel arm (19.9%) compared to the paclitaxel arm (44.3%, p<0.001), which were mostly due to organizational reasons (11.4 vs 24.6%, p=0.003). Dose reductions were observed in 9.6% patients in the cabazitaxel arm compared to 11.4% in the paclitaxel arm (p=0.721). Main reason for dose reductions were non-hematological toxicities in 3.0 vs 7.8% (p=0.087), respectively.

CONCLUSIONS:

The GENEVIEVE study showed no short-term effect of cabazitaxel in TNBC or luminal B/HER2- primary breast cancer, while there seemed to be no differences in drug exposure and patient compliance between the two arms.

Date of the Report:

30th April 2016