CLINICAL STUDY REPORT

- SYNOPSIS -

Investigating Denosumab as an add-on to neoadjuvant chemotherapy in RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-Paclitaxel schedules in a 2x2 factorial design (GeparX)

EudraCT No.: 2015-001755-72

Investigational Products:	**Denosumab, nab-Paclitaxel, ABP 980**
Indication:	**Neoadjuvant treatment of primary breast cancer**
Study Protocol:	**GBG 88 (including Protocol Amendment 3, Version 11.04.2019)**
Phase:	**Phase IIb**
Report Version:	**Final Version V2.0**
First Patient Enrolled:	February 13, 2017
Last Patient Completed:	January 06, 2020
Coordinating Investigator:	Prof. Dr. Jens-Uwe Blohmer Charité – Universitätsmedizin Berlin Charitéplatz 1 10113 Berlin, Germany
Sponsor:	GBG Forschungs GmbH Martin-Behaim-Straße 12 63263 Neu-Isenburg, Germany
Date of this report:	December 17, 2020
Date of any previous reports:	V 1.0, November 13, 2020

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1. 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:	Volume:	
Name of active ingredient:	Page:	

Title of Study:

Investigating Denosumab as an add-on to neoadjuvant chemotherapy in RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-Paclitaxel schedules in a 2x2 factorial design (GeparX)

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Name of finished product:	Volume:	
Name of active ingredient:	Page:	

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

Publication (reference):

Kümmel S, von Minckwitz G, Nekljudova V, et al. Investigating Denosumab as add-on neoadjuvant treatment for hormone receptor-negative, RANK-positive or RANK-negative primary breast cancer and two different nab-Paclitaxel schedules - 2x2 factorial design (GeparX). J Clin Oncol 2016; 34.15_suppl.TPS635.

Kümmel S, von Minckwitz G, Vladimirova V, et al. Investigating Denosumab as an add-on neoadjuvant treatment for RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-Paclitaxel schedules - 2x2 factorial design (GeparX). 38. Jahrestagung Deutsche Gesellschaft für Senologie 2018; P029.

Kümmel S, Wimberger P, von Minckwitz G, et al. Investigating denosumab as an add-on neoadjuvant treatment for RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-Paclitaxel schedules - 2x2 factorial design (GeparX) – an interim safety analysis. J Clin Oncol 2018; 36.15_suppl.569.

Denkert C, Link T, Jank P, et al. Comparison of an automated cartridge-based system for mRNA assessment with central immunohistochemistry in the neoadjuvant GeparX trial. J Clin Oncol 2019; 37.15_suppl.3075

Blohmer JU, Link T, Kümmel S et al. Investigating denosumab as an add-on treatment to neoadjuvant chemotherapy and two different nab-Paclitaxel schedules in a 2x2 design in primary breast cancer - First results of the GeparX study. Cancer Res 2020;80(4 Suppl):Abstract GS3-01

Wimberger P, Blohmer J-U, Krabisch P, et al. Influence of denosumab on disseminated tumor cells (DTC) in the bone marrow of breast cancer (BC) patients with neoadjuvant treatment – a GeparX translational substudy. J Clin Oncol 2020; 38.15_suppl.580

Link T, Blohmer J-U, Just M, et al. Denosumab as add-on to different regimen of nab-paclitaxel-anthracycline based neoadjuvant chemotherapy in early breast cancer: Subgroup analyses by RANK expression and HR status. Ann Oncol 2020; 31:suppl.4:308-9

Studied Period (years):

Date of the first patient enrolled: **13 February 2017**

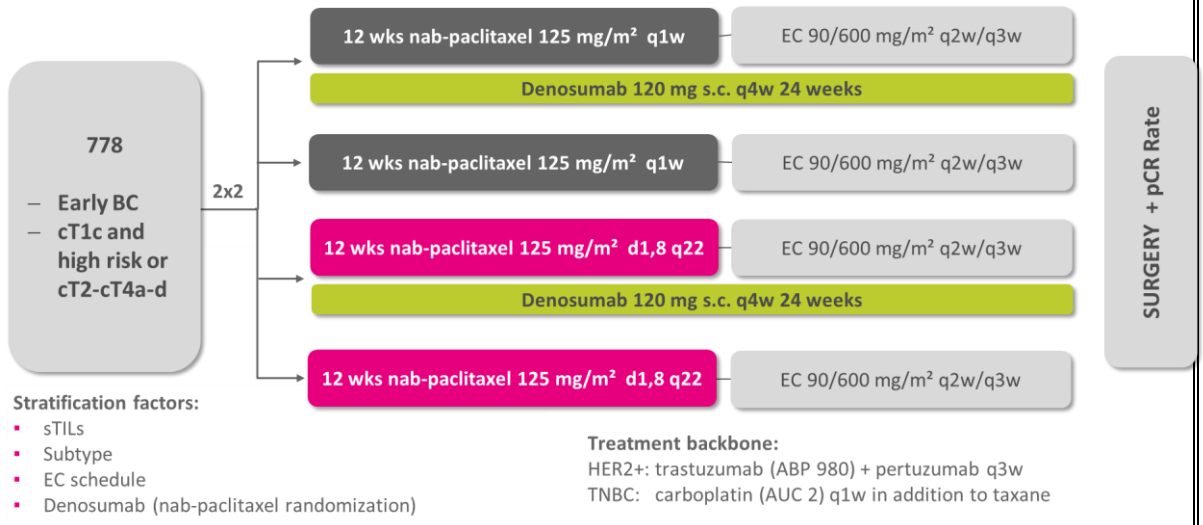
Date of the last patient completed (or data cut-off date): **06 January 2020**

Phase of Development:

Phase IIb

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

GeparX Trial Design



Objectives:

Co-Primary Objectives:

- To compare the pathological complete response (pCR, ypT0 ypN0) rates of neoadjuvant treatment with or without denosumab in addition to backbone treatment consisting of nab-Paclitaxel 125mg/m² weekly (plus carboplatin in triple-negative disease) followed by epirubicin/cyclophosphamide or of nab-Paclitaxel 125mg/m² day 1,8 q22 (plus carboplatin in triple-negative disease) followed by epirubicin/cyclophosphamide plus anti-HER2 treatment (i. e. trastuzumab/pertuzumab in case of positive HER2-status) in patients with early breast cancer.
- To compare the pCR (ypT0 ypN0) rates of nab-Paclitaxel 125mg/m² weekly (plus carboplatin in triple-negative disease) followed by epirubicin/cyclophosphamide or nab-Paclitaxel 125mg/m² day 1,8 q22 (plus carboplatin in triple-negative disease) followed by epirubicin/cyclophosphamide plus anti-HER2 treatment (i. e. trastuzumab/pertuzumab in case of positive HER2-status) in patients with early breast cancer.

Secondary Objectives:

- To test for interaction of denosumab treatment with RANK expression (cutoff for RANK expression high vs low as defined in the statistical analysis plan).
- To assess the pCR rates per arm in subgroups according to stratification (minimization) factors.
- To assess the pCR rates per arm for patients with RANK high and RANK low prospectively and centrally by immunohistochemistry.
- To determine the rates of ypT0/Tis ypN0; ypT0 ypN0/+; ypT0/Tis ypN0/+; ypT(any) ypN0 for both randomizations.
- To determine the response rates of the breast tumor and axillary nodes based on physical examination and imaging tests (sonography, mammography, or MRI) after treatment in both arms for each

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

randomization.

- To determine the breast conservation rate after each treatment.
- To assess the toxicity and compliance, including time to onset of peripheral sensory neuropathy grade 2-4 and resolution of peripheral sensory neuropathy grade 2-4 to grade ≤1.
- To determine loco-regional invasive recurrence free survival (LRRFS), distant-disease-free survival (DDFS), invasive disease-free survival (iDFS), EFS (event free survival) and overall survival (OS) for all treatment arms and according to stratified subpopulations.
- To compare RANK/L expression from baseline to surgery.
- To compare Ki-67 from baseline to surgery.
- To correlate response (complete vs. partial vs. no change) measured by best appropriate imaging method after the first two cycles of treatment with pCR.
- To assess mammographic density–changes induced by denosumab.
- To assess quality of life with a focus on persisting peripheral sensory neuropathy using the FACT-Taxane (Version 4) questionnaire.

Objectives of substudies:

ABP 980 (HER2+) substudy:

Co-Primary:

- To assess the pCR (ypT0 ypN0) rate of neoadjuvant treatment with ABP 980 and pertuzumab in the overall HER2+ cohort and compare with the results obtained in GeparSepto study.
- To compare the pCR (ypT0 ypN0) rate of nab-Paclitaxel 125mg/m² weekly → epirubicin/cyclophosphamide or nab-Paclitaxel 125mg/m² day 1,8 q22 → epirubicin/cyclophosphamide plus anti-HER2 treatment (i.e. ABP 980/ pertuzumab in case of positive HER2-status) in patients with early breast cancer.

Secondary:

- To assess the pCR rates in HER2+ patients treated with ABP 980 in subgroups according to HR status.
- To assess the pCR rate in subgroups by denosumab.
- To determine the pCR rates in the overall HER2+ cohort of ypT0/Tis ypN0; ypT0 ypN0/+; ypT0/Tis ypN0/+; ypT(any) ypN0 for both randomizations.
- To determine the response rates on the HER2+ cohort of the breast tumor and axillary nodes based on physical examination and imaging tests (sonography, mammography, or MRI) after treatment in both arms for each randomization.
- To determine the breast conservation rate in the HER2+ cohort.
- To assess the toxicity and compliance for the HER2+ cohort treated with ABP 980 and by systemic therapy (nab-Paclitaxel 125mg/m² continuously vs. 2/3; epirubicin/cyclophosphamide, Denosumab yes vs. no).
- To specifically address the incidence of diarrhoea and cardiovascular events.
- To assess the toxicity with EC and ABP 980/pertuzumab.
- To determine loco-regional invasive recurrence free survival (LRRFS), distant-disease-free survival (DDFS), invasive disease-free survival (iDFS), EFS (event free survival) and overall survival (OS) for all

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

HER2+ patient treated with ABP 980/pertuzumab.

Disseminated tumor cells (DTC) substudy (translational)

- **Primary:** Does the application of denosumab in terms of an add-on neoadjuvant treatment eradicate DTCs in the bone marrow of breast cancer patients?
- **Secondary:** Does a potential eradication of DTC by add-on neoadjuvant denosumab treatment influence the rate of pCR?

Methodology:

This is a multicenter, prospective, 2x2 randomized, open-label phase IIb study to compare neoadjuvant treatment with and without denosumab in patients with untreated breast cancer and two different nab-Paclitaxel schedules.

Patients were first randomized (using Pocock minimization) to either denosumab or no denosumab in addition to neoadjuvant therapy. Stratification (minimization) factors for randomization were lymphocyte-predominant breast cancer (LPBC, negative defined as ≤50% stromal tumor infiltrating lymphocytes vs present defined as >50% stromal tumor infiltrating lymphocytes), subtype (HER2-negative, hormone-receptor-positive vs triple-negative breast cancer vs. HER2-positive), and epirubicin/cyclophosphamide treatment (every two weeks vs every 3 weeks).

Secondarily patients were randomized (using Pocock minimization) to nab-Paclitaxel 125mg/m² weekly (plus carboplatin in case of triple-negative disease) followed by epirubicin/cyclophosphamide or nab-Paclitaxel 125mg/m² day 1, 8 q22 (plus carboplatin in case of triple-negative disease) followed by epirubicin/cyclophosphamide.

The first randomization (denosumab) was an additional minimization factor for the second randomization (chemotherapy regimen).

The HER2+ substudy was a cohort study investigating open label non-randomized use of ABP 980 in combination with pertuzumab.

In all study arms, treatment was given until surgery, disease progression, unacceptable toxicity, withdrawal of consent of the patient, or termination by the Sponsor.

The Protocol Board (Subboard Neoadjuvant) and the Independent Data Monitoring Committee reviewed and monitored the conduct of the study.

Number of patients (planned and analyzed):

planned: **778**, screened: 1016, randomized: 780, analyzed (safety): 768, analyzed (efficacy): **780**

Diagnosis and Main Criteria for Inclusion:

The study included patients of at least 18 years of age, with a Karnofsky Performance status index ≥ 90%, unilateral or bilateral primary carcinoma of the breast histologically confirmed by core biopsy and measurable disease (i.e. tumor lesion in the breast or the nodes measurable in two dimensions, preferably by sonography). Patients had to have stages cT2 - cT4a-d or cT1c with either cN+ or pNSLN+ or estrogen receptor (ER)-neg/ progesterone receptor (PR)-neg or Ki-67>20% or HER2-pos.

Patients were eligible with centrally confirmed ER-, PR- and HER2-status. Central pathology also included

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

assessment of Ki-67, TIL and RANK/L status on core biopsy. TNBC was defined as ER<1% and PR<10% stained cells and HER2-negative; and HER2-positive was defined as IHC 3+ or in-situ hybridization (ISH) and according to ASCO-CAP guidelines as of 2013. Lymphocyte predominant breast cancer (LPBC) was defined as more than 50% stromal tumor infiltrating lymphocytes. Patients were eligible for the HER2+ substudy if they had a centrally confirmed HER2+ tumor.

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

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

Investigational products in this study were Denosumab (XGEVA®), nab-Paclitaxel (Abraxane®), and (for patients with HER2-positive disease) trastuzumab (ABP 980).

Denosumab

- Dose: 120 mg

  Supplementation of at least 500 mg calcium and 400 IU vitamin D was required in all patients, unless hypercalcemia was present. If hypocalcemia occurred, short-term augmentation of calcium.
- Application: s.c. into the thigh, abdomen or upper arm.
- Schedule: day 1 (+/- 3 days) every 4 weeks for 6 cycles.

  First injection was to be given on day 2 after the administration of anti-HER2 treatments.
- Batch numbers provided: 1075133, 1076506, 1089330, 1090728, 1092392, 1094478, 1096918

nab-Paclitaxel

- Dose: 125 mg/m²
- Application: i.v. over 30-60 min.
- Schedule: on days 1, 8, 15 every 3 weeks for 4 cycles or days 1, 8 every 3 weeks for 4 cycles
- Batch numbers provided: 16F1574, 17F0042, 17F0086, 17F0308, 18F0040, 18F0161, 18F0359, 18F0620

Trastuzumab (ABP 980).

- Dose: Loading dose: 8 mg/kg body weight at the first infusion; Maintenance dose: 6 mg/kg body weight
- Application: i.v. over 90 min for loading dose (monitor patient for 4.5 h afterwards) and over 30-90 min for maintenance dose (monitor patient for 30 min afterwards).
- Schedule: First injection was to be given the day before the application of nab-Paclitaxel and denosumab. Following injections on day 1 q day 22 for 8 cycles (8 infusions) together with nab-Paclitaxel- epirubicin/cyclophosphamide
- Batch numbers provided: 1081653, 1083798, 1092412, 1094298, 1096124, 1099117

Non-investigational products in this study were Epirubicin, Cyclophosphamide, Carboplatin (for patients with TNBC only), and Pertuzumab (for patients with HER2-positive disease).

Epirubicin

- Dose: 90 mg/m²
- Application: i.v. over at least 30 min via an implanted port system or catheter to the subclavian vein
- Schedule: on day 1 every 2 or 3 weeks for 4 cycles

Cyclophosphamide

- Dose: 600 mg/m²
- Application: i.v. over 60 min.
- Schedule: on day 1 every 2 or 3 weeks for 4 cycles. Cyclophosphamide was to be given on the same days

as epirubicin after the end of the epirubicin infusion.

Carboplatin

- Dose: AUC 2.0
- Application: i.v. over 15 - 60 min.
- Schedule: on day 1, 8, 15 every 3 weeks for 4 cycles Carboplatin should be given on the same days as nab-Paclitaxel and after the end of nab-Paclitaxel infusion.

Pertuzumab

- Dose: Loading dose 840mg, maintenance dose 420mg
- Application: i.v.
- Schedule: Loading dose on the day before the first nab-Paclitaxel cycle and denosumab administration, maintenance dose on day 1 q day 22 for a minimum of 4 cycles (acsording to label)

Duration of Treatment:

The entire treatment period was 24 weeks. Denosumab was given every 4 weeks throughout; nab-Paclitaxel was given for 12 weeks, afterwards epirubicin and cyclophosphamide were given every 2 or 3 weeks for 12 weeks. Time to surgery after treatment should not exceed 2 months.

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

See above for details on therapy and dose.

Criteria for Evaluation:

Efficacy:

Primary endpoint

The primary efficacy endpoint of this study was pCR of breast and lymph nodes (ypT0 ypN0), defined as no microscopic evidence of residual invasive and no non-invasive viable tumor cells in all resected specimens of the breast and axilla.

Secondary endpoints:

Short term secondary efficacy endpoints were:

- ypT0/Tis ypN0, ypT0 ypN0/+, ypT0/Tis ypN0/+, ypT(any) ypN0
- Clinical (c) and imaging (i) response assessed every 2nd cycle and before surgery by physical examination and imaging tests with response assessed as complete, partial, stable, or progression.
- Breast conservation defined as tumorectomy, segmentectomy or quadrantectomy as the most radical surgery.
- Axilla conservation defined as sentinel node biopsy (SNB) only (before or after chemotherapy).
- Mammographic density score

Long-term secondary efficacy (invasive disease-free survival, event free survival, loco-regional invasive recurrence free interval, distant-disease-free survival, and overall survival for all treatment arms and

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

according to stratified subpopulations) is not part of this report and will be analyzed with sufficient follow up data at a later time point.

Tolerability and Safety:

Secondary endpoints included descriptive statistics for the 4 treatments (+/- anti-HER2-treatment) given on the number of patients whose treatment had to be reduced, delayed or permanently stopped. The reason for termination included aspects of efficacy (e.g. termination due to tumor progression), safety (e.g. termination due to adverse events) and compliance (e.g. termination due to patient's withdrawal of consent). Reasons for premature termination were categorized according to the main reason and presented in frequency tables. Safety by toxicity grades were defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Corresponding safety endpoints were:

- Toxicity (adverse events) reported for the whole treatment duration and for the nab-Paclitaxel and EC portion of the treatment separately. Congestive heart failure was assessed by NYHA class. LVEF assessment had to be performed according to guidelines for anti-HER2 treatment and anthracyline therapy (e.g. after taxane and prior to surgery); LVEF decreased by ≥10% and to <50% was reported.
- Time of onset of grade 2-4 peripheral sensory neuropathy was defined as the first cycle in which the peripheral sensory neuropathy of grade ≥2 occurred; additionally, time to onset of grade 3-4 peripheral sensory neuropathy was considered.
- Time of resolution of grade 2-4 peripheral sensory neuropathy to at least grade 1 was defined as time in weeks between first occurrence of grade 2-4 peripheral sensory neuropathy and its resolution to grade ≤1. Patients in which peripheral sensory neuropathy persisted grade ≥2 were censored at the date of end of treatment. Additionally, time to resolution of grade 3-4 peripheral sensory neuropathy was analyzed.

Corresponding compliance endpoints were:

- premature treatment discontinuations (with reasons)
- dose reductions (with reasons)
- treatment delays (with reasons)
- treatment interruptions (skipped infusions, with reasons)
- additionally, for nab-Paclitaxel d1, 8 q22 arm not respecting the pause in week 3 was reported as well as any case of overdose
- Relative total dose and relative total dose intensity.

Substudy endpoints

Primary efficacy endpoint ABP980 (HER2+) substudy:

The primary efficacy endpoint of this substudy was pCR of breast and lymph nodes (ypT0 ypN0), as defined in the main protocol.

Secondary short-time efficacy endpoints ABP980 (HER2+) substudy:

All Secondary short-time efficacy endpoints of this substudy correspond to endpoints as defined in the main protocol.

AEs of special interest for this substudy were: Cardiac failure, infusion reactions, pulmonary toxicity,

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

hypersensitivity, infections and infestations.

Endpoints of DTC substudy:

To assess endpoints of the DTC substudy, bone marrow samples were collected at baseline (before the beginning of neoadjuvant chemotherapy). Subsequently, patients in both arms with confirmed DTC-positivity at baseline were subjected to a single follow-up bone marrow aspiration within surgery.

The corresponding primary endpoint was the absence of DTCs after neoadjuvant treatment in patients with DTCs detected at baseline. The second endpoint was pCR (primary definition) as defined in the main protocol.

Statistical Methods:

An 'intent-to-treat' (ITT) analysis was conducted for all patients randomized in the study. In addition, a 'per-protocol' analysis was conducted.

All HER2+ patients were analyzed for subgroups and multivariate analyses of the main study irrespective of the anti-HER2 treatment according to the general ITT principles.

Sample size :

The sample size calculation was based on the following assumptions for the primary endpoint:

- Improvement of the pCR rate by denosumab in all patients from 35% to 46% (odds ratio, OR=1.58)
- Improvement of the pCR rate by different schedules of chemotherapy (nab-Paclitaxel 125 mg/m^2 day 1,8 q22 (carboplatin) → epirubicin/cyclophosphamide arm to nab-Paclitaxel 125 mg/m^2 weekly (carboplatin) → epirubicin/cyclophosphamide) from 36% to 45% (OR=1.45)

The primary continuity corrected χ2-test of pCR rates between denosumab and no denosumab arms had 92% power to the 2-sided significance level α=0.10. The continuity corrected χ2-test of pCR rates between nab-Paclitaxel 125 mg/m^2 weekly (carboplatin) → epirubicin/cyclophosphamide to nab-Paclitaxel 125 mg/m^2 day 1,8 q22 (carboplatin) → epirubicin/cyclophosphamide arms had 80% power to the 2-sided significance level α=0.10.

It is planned to recruit 778 subjects into this study.

The sample size calculation for the HER2+ substudy was based on the primary endpoint of the main study:

All patients with HER2+ disease enrolled into the study received ABP 980 in addition to pertuzumab and backbone chemotherapy.

It was planned to recruit approximately 150 subjects into this substudy.

All study patients were supposed to be subjected to DTC analysis. Given the expected frequency of DTC-positivity (roughly 40%), approx. 310 patients were expected to be eligible for additional follow-up aspiration, resulting in approximately 600 DTC analyses in total.

Sample size for the continuity corrected χ2-test was computed using nQuery Advisor 6.02.

Primary efficacy endpoint analysis:

Co-primary objectives were tested according to the improved Bonferroni procedure: the smaller of the two

p-values was compared with α = 0.1 and the larger p-value was compared with α = 0.2 to keep the overall significance level of the study of α = 0.2.

The primary endpoint was summarized as pathological complete response rate for each treatment group for both randomizations. Two-sided 90% confidence intervals were calculated according to Pearson and Clopper. The difference in the rates of pathological complete response was evaluated as rate difference (denosumab arm minus no-denosumab arm; nab-Paclitaxel 125 mg/m^2 weekly (carboplatin) → epirubicin/cyclophosphamide minus nab-Paclitaxel 125 mg/m^2 day 1,8 q22 (carboplatin) → epirubicin/cyclophosphamide) with 90% confidence interval. Additionally, an odds ratio with the 90% confidence interval was reported. The significance was tested with the two-sided continuity corrected χ2-test according to the improved Bonferroni procedure.

The null hypothesis was that there was no difference in pCR rates between treatment arms; the alternative hypothesis was that there was a difference for both randomizations.

The significance level for all other tests was set to 2-sided α = 0.05. There was no adjustment for multiple comparisons in the analyses for the stratified subpopulations. A secondary logistic regression analysis correcting for the minimization factors was conducted for the primary endpoint.

Uni- and multivariate logistic regression were performed for pCR to adjust for the known factors (treatment group for both randomizations, minimization factors, age, tumor size, nodal status, grade, histological type), based on the ITT population.

Additionally, a multivariate logistic regression including all factors above and interaction between denosumab and chemotherapy arms was performed.

Secondary efficacy endpoint analysis:

Secondary short-time efficacy endpoints (ypT0/Tis ypN0; ypT0 ypN0/+; ypT0/Tis ypN0/+; ypT(any) ypN0, response by physical examination, imaging response, breast conservation) were also summarized as rates in each treatment group, two-sided 95% confidence intervals were calculated according to Pearson and Clopper, and the continuity corrected Pearson χ2 test was performed to evaluate the difference of rates in treatment arms; these tests were considered explorative. The significance level for all tests was set to 2-sided α = 0.05. Subgroup and multivariate analyses were performed for ypT0/Tis ypN0 in the same way as for the primary endpoint.

A Breslow-Day test for interaction was performed to asses difference of treatment effect between high RANK and low RANK subgroups (the cutpoint was defined in statistical analysis plan) with 2-sided α = 0.1. The null hypothesis was that the odds ratios of pCR in denosumab arm to no denosumab arm were equal in the RANK+ and RANK-subgroups, the alternative hypothesis was that odds ratios were not equal.

For long-term secondary efficacy endpoints that will be analyzed with sufficient follow-up data at a later time point, survival curves will be estimated using the Kaplan-Meier method, based on the mITT population. 3-year and 5-year survival (and 95%CIs) will be estimated. Univariate and multivariate Cox-proportional hazards model will be used to adjust hazard ratios for minimization factors and the above defined covariates.

Tolerability and Safety

Frequencies of patients whose treatment had to be reduced, delayed or permanently stopped were given for the 4 treatments (+/- anti-HER2-treatment). The reason for termination included aspects of efficacy (e.g. termination due to tumor progression), safety (e.g. termination due to adverse events) and compliance (e.g.

termination due to patient's withdrawal of consent).

Time to the first occurrence of grade 2-4 peripheral neuropathy and time to improvement of peripheral neuropathy were analyzed using Kaplan-Meier curves and log-rank test.

Endpoints HER2+ substudy:

Primary and secondary objectives for the HER2+ substudy were assessed in all patients who have received at least one dose of ABP 980. The pCR rates with a 95% CI were reported and compared between chemotherapy treatment arms using the continuity corrected $\chi 2$-test. Safety and compliance for HER2+ substudy was reported descriptively in treatment arms.

Endpoints DTC substudy:

DTC presence at baseline was presented in a frequency table per denosumab arm and overall for all patients evaluated in the DTC substudy.

In the patients DTC positive at baseline the eradication after neoadjuvant chemotherapy was presented per denosumab arm and overall and compared between arms with the exact test of Fisher. pCR rates were presented in the patients DTC positive at baseline according to the eradication after neoadjuvant chemotherapy and compared with the exact test of Fisher.

SUMMARY

Efficacy Results:

There was no difference in pCR (ypT0 ypN0) rates between denosumab arms (denosumab: 41.0%, no denosumab: 42.8%, p=0.582). nab-Paclitaxel weekly resulted in significantly (to the significance level of α=0.1) higher pCR (ypT0 ypN0) rates compared to nab-Paclitaxel d1,8 q22 (nab-Paclitaxel weekly: 44.9%, nab-Paclitaxel d1,8 q22: 39.0%, p=0.062).

Table: Primary endpoint pCR (ypT0 ypN0), ITT set, denosumab randomization

pCR (ypT0 ypN0)	Denosumab N=390 N(%)	No denosumab N=390 N(%)	Overall N=780 N(%)	p-value stratified*	p-value unstratified
yes	160 (41.0)	167 (42.8)	327 (41.9)	0.582	0.663
no	230 (59.0)	223 (57.2)	453 (58.1)		
90% CI	(36.9%, 45.1%)	(38.7%, 46.9%)			
95% CI	(36.1%, 45.9%)	(37.9%, 47.7%)			

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

Table: Primary endpoint pCR (ypT0 ypN0), ITT set, nab-Paclitaxel randomization

pCR (ypT0 ypN0)	nP weekly N=390 N(%)	nP d1,8 q22 N=390 N(%)	Overall N=780 N(%)	p-value stratified*	p-value unstratified
yes	175 (44.9)	152 (39.0)	327 (41.9)	0.062	0.110
no	215 (55.1)	238 (61.0)	453 (58.1)		
90% CI	(40.7%, 49.0%)	(34.9%, 43.0%)			
95% CI	(39.9%, 49.8%)	(34.1%, 43.8%)			

Multivariate logistic regression analyses adjusted for stratification factors revealed that denosumab (denosumab vs no denosumab: OR 0.90, 90% CI 0.70-1.16, 95% CI 0.66-1.22, p=0.489) did not predict for achievement of higher pCR (ypT0 ypN0). However, nP weekly (nP weekly vs nP d1,8 q22: OR 1.33, 90% CI 1.03-1.71, 95% CI 0.98-1.80, p=0.071) predicted (to the significance level of α=0.1) for achievement of pCR (ypT0 ypN0), confirming primary analysis.

Multivariate logistic regression analyses including additional factors confirmed results of univariate analyses: treatment with denosumab (denosumab vs no denosumab: OR 0.92, 90% CI 0.71-1.20, 95% CI 0.67-1.27, p=0.614) was not predictive for achievement of pCR (ypT0 ypN0), but treatment with nab-Paclitaxel (to the significance level of α=0.1) (nP weekly vs nP d1,8 q22: OR 1.36, 90% CI 1.04-1.78, 95% CI 0.99-1.87, p=0.057) was. The test for interaction between denosumab and nab-paclitaxel randomization was negative (p=0.275) in the multivariate model.

Logistic regression analysis in subgroups confirmed that treatment with nab-Paclitaxel weekly was predictive for pCR (ypT0 ypN0) in the subgroups of TNBC (nab-Paclitaxel weekly vs nab-Paclitaxel d1,8 q22 OR 1.52, 90% CI 1.05-2.21, 95% CI 0.976-2.38, p=0.064), EC 2-weekly (nab-Paclitaxel weekly vs nab-Paclitaxel d1,8 q22 OR 1.52, 90% CI 1.09-2.11, 95% CI 1.03-2.25, p=0.037), and denosumab nab-Paclitaxel weekly vs nab-Paclitaxel d1,8 q22 OR 1.82, 90% CI 1.29-2.56, 95% CI 1.21-2.74, p=0.004, test for interaction p=0.016). There was no adjustment for multiple comparisons and results have to be interpreted with caution.

There was no difference in pCR (ypT0 ypN0) in subgroups according to RANK expression, neither between the denosumab, nor between the nab-paclitaxel arms. Treatment was not predictive for pCR (ypT0 ypN0) in subgroups according to RANK (RANK low: denosumab vs no denosumab OR 1.10 (95% CI 0.78-1.56), p=0.589, RANK high: OR 0.86 (0.44-1.68), p=0.667; test for interaction p=0.528; RANK low: nab-Paclitaxel d1,8 q22 vs nab-Paclitaxel weekly OR 1.19 (0.84-1.69), p=0.318, RANK high: OR 1.30 (0.67-2.52), p=0.447, test for interaction: 0.833).

Table: Summary of pCR definitions ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT0(any) ypN0, denosumab randomization

Secondary endpoint definitions of pCR	Denosumab N=390 N(%)	No Denosumab N=390 N(%)	Overall N=780 N(%)	p-value*	p-value unstratified
ypT0/is, ypN0					
yes	179 (45.9)	189 (48.5)	368 (47.2)	0.436	0.519

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

no	211 (54.1)	201 (51.5)	412 (52.8)		
90% CI	(41.7%, 50.0%)	(44.3%, 52.6%)			
95% CI	(41.0%, 50.8%)	(43.5%, 53.4%)			
ypT0, ypN0/+					
yes	166 (42.6)	181 (46.4)	347 (44.5)	0.220	0.313
no	224 (57.4)	209 (53.6)	433 (55.5)		
90% CI	(38.4%, 46.7%)	(42.3%, 50.6%)			
95% CI	(37.7%, 47.5%)	(41.5%, 51.4%)			
ypT0/is, ypN0/+					
yes	190 (48.7)	208 (53.3)	398 (51.0)	0.150	0.223
no	200 (51.3)	182 (46.7)	382 (49.0)		
90% CI	(44.6%, 52.9%)	(49.2%, 57.5%)			
95% CI	(43.8%, 53.7%)	(48.4%, 58.3%)			
ypT(any), ypN0					
yes	291 (74.6)	297 (76.2)	588 (75.4)	0.588	0.678
no	99 (25.4)	93 (23.8)	192 (24.6)		
90% CI	(71.0%, 78.2%)	(72.6%, 79.7%)			
95% CI	(70.3%, 78.9%)	(71.9%, 80.4%)			

Table Summary of secondary pCR definitions ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT0(any) ypN0, nab-Paclitaxel randomization

Secondary endpoint definitions of pCR	nP weekly N=390 N(%)	nP d1,8 q22 N=390 N(%)	Overall N=780 N(%)	p-value*	p-value unstratified
ypT0/is, ypN0					
yes	197 (50.5)	171 (43.8)	368 (47.2)	0.043	0.073
no	193 (49.5)	219 (56.2)	412 (52.8)		
90% CI	(46.3%, 54.7%)	(39.7%, 48.0%)			
95% CI	(45.6%, 55.5%)	(38.9%, 48.8%)			
ypT0, ypN0/+					
yes	185 (47.4)	162 (41.5)	347 (44.5)	0.055	0.113
no	205 (52.6)	228 (58.5)	433 (55.5)		
90% CI	(43.3%, 51.6%)	(37.4%, 45.6%)			
95% CI	(42.5%, 52.4%)	(36.6%, 46.4%)			

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

ypT0/is, ypN0/+					
yes	214 (54.9)	184 (47.2)	398 (51.0)	0.017	0.038
no	176 (45.1)	206 (52.8)	382 (49.0)		
90% CI	(50.7%, 59.0%)	(43.0%, 51.3%)			
95% CI	(49.9%, 59.8%)	(42.2%, 52.1%)			
ypT(any), ypN0					
yes	302 (77.4)	286 (73.3)	588 (75.4)	0.261	0.212
no	88 (22.6)	104 (26.7)	192 (24.6)		
90% CI	(74.0%, 80.9%)	(69.7%, 77.0%)			
95% CI	(73.3%, 81.6%)	(68.9%, 77.7%)			

There was no difference in any of the pCR definitions (ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT0(any) ypN0) analyzed as secondary endpoints between denosumab arms. Nab-paclitaxel weekly resulted in significantly higher pCR rates compared to nab-Paclitaxel d1,8 q22 when pCR was defined as ypT0/is, ypN0 (nab-Paclitaxel weekly: 50.5%, nab-Paclitaxel d1,8 q22: 43.8%, p=0.043), and ypT0/is, ypN0/+ (nab-Paclitaxel weekly: 54.9%, nab-Paclitaxel d1,8 q22: 47.2%, p=0.017).

There were no significant differences in overall clinical (imaging) response rate (ORR, defined as complete or partial response) of the breast after two cycles of treatment (ORR denosumab 74.6%, no denosumab 78.2%, p=0.245; nab-Paclitaxel weekly: 79.0%, nab-Paclitaxel d1,8 q22: 73.8%, p=0.074) or before surgery (ORR denosumab 85.6%, no denosumab 90.3%, p=0.058; nab-Paclitaxel weekly: 89.0%, nab-Paclitaxel d1,8 q22: 86.9%, p=0.303) between arms in any of the two randomizations.

Breast conservation rates (denosumab 70.4%, no denosumab 76.1%, p=0.078; nab-Paclitaxel weekly: 74.5%, nab-Paclitaxel d1,8 q22: 72.1%, p=0.444), and axilla conservation rates (denosumab 62.5%, no denosumab 64.7%, p=0.562; nab-Paclitaxel weekly: 62.7%, nab-Paclitaxel d1,8 q22: 64.5%, p=0.504), were similar between arms in the two randomizations. Mammographic density–changes induced by denosumab were only marginal and not significantly different.

Efficacy Conclusions

In a 2x2 design pCR rates after neoadjuvant chemotherapy with and without Denosumab and two different schedules of nab-Paclitaxel were investigated. A total of 780 patients were randomized and were included in the ITT set (195 patients in each of the 4 treatment arms). Study patient and tumor characteristics are well balanced between all 4 treatment arms with no relevant differences. Overall, patients were relatively young with median 49 years (range 22-80) and therefore most patients were premenopausal. In addition, there were no significant differences at baseline in patients' general medical history, in co-medication as well as in cardiac assessments between arms in any of the two randomizations.

The primary efficacy endpoint was pCR (ypT0 ypN0) for each treatment group for both randomizations. There was no significant difference in pCR rates between with or without Denosumab (denosumab: 41.0%, no denosumab: 42.8%, p=0.582). However, the pCR rate of weekly nab-Paclitaxel was significantly higher (to the significance level of 0.1) than of the nab-Paclitaxel schedule d1,8 q22 with an absolute and clinically meaningful difference of 5.9% (nab-Paclitaxel weekly: 44.9%, nab-Paclitaxel d1,8 q22: 39.0%, p=0.062). In patients with TNBC the pCR rate was statistically significantly higher with the nab-Paclitaxel weekly schedule

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

(nab-Paclitaxel weekly: 60.4%, nab-Paclitaxel d1,8 q22: 50.0%, p=0.056) whereas in the hormone-receptor and HER2-positive group there were no significant differences between both nab-Paclitaxel schedules. In addition, the pCR rate was statistically significantly higher with nab-Paclitaxel weekly followed by EC 2-weekly (nab-Paclitaxel weekly: 46.9%, nab-Paclitaxel d1,8 q22: 36.7%, p=0.038), and with nab-Paclitaxel weekly and in combination with denosumab treatment (nab-Paclitaxel weekly: 48.2%, nab-Paclitaxel d1,8 q22: 33.8%, p=0.027); however, the test for interaction between denosumab and nab-paclitaxel randomization was negative (p=0.275) in the multivariate model. It should also be noted that there was no adjustment for multiple comparisons and results of the subgroup analysis have to be interpreted with caution.

There was no difference in any other pCR definitions analyzed as secondary endpoints between denosumab arms whereas nab-paclitaxel weekly resulted in significantly higher rates when pCR was defined as ypT0/is, ypN0 (nab-Paclitaxel weekly: 50.5%, nab-Paclitaxel d1,8 q22: 43.8%, p=0.043) and ypT0/is, ypN0/+ (nab-Paclitaxel weekly: 54.9%, nab-Paclitaxel d1,8 q22: 47.2%, p=0.017).

Additionally, the primary endpoint pCR was analyzed in the subgroups according to RANK high vs low expression for both randomizations. There was no difference according to RANK expression, neither between the denosumab, nor between the nab-paclitaxel arms. Likewise, there were no significant differences concerning clinical response in the breast, breast conservation rate as well as axillary surgery surgery between arms in any of the two randomizations.

In conclusion, in the GeparX study the addition of denosumab to neoadjuvant chemotherapy did not increase the pCR rate in early breast cancer. nab-Paclitaxel 125mg/m² weekly resulted in a significantly higher pCR rate than given d1,8 q22. In TNBC patients, optimized neoadjuvant chemotherapy with nab-paclitaxel 125mg/m² weekly plus carboplatin followed by EC achieves a pCR rate of 60.4%. This is an exceptionally high pCR rate without any additional targeted agents. Studies using a checkpoint inhibitor report pCR rates of maximum 64% at a higher rate of toxicity.

Safety Results:

There was no difference in terms of chemotherapy treatment discontinuation between denosumab arms. Significantly more patients receiving nab-paclitaxel weekly discontinued treatment with nab-Paclitaxel (20.5% vs 6.2%, p<0.001). Similarly, chemotherapy dose delays and dose reductions did not differ significantly between denosumab arms. Dose delays (76.2% vs 56.0%, p<0.001) and reductions (26.1% vs 11.5%, p<0.001) of nab-Paclitaxel, as well as dose reductions of EC (23.6% vs 15.7%, p=0.009) were all significantly more common in the nab-Paclitaxel weekly arm.

In the overall safety population, all patients experienced at least one adverse event of any grade during treatment. Regarding the denosumab randomization, there were no significant differences between arms in any of the predefined adverse event categories. Within the nab-Paclitaxel randomization, no differences were seen in terms of any high-grade adverse events, any grade and high-grade hematological, and any grade non-hematological adverse events. High-grade non-hematological adverse events were significantly more frequent in the nab-Paclitaxel weekly arm compared to the nab-Paclitaxel d1,8 q22 arm (33.7% vs 24.1%, respectively, p=0.004). A total of 218 patients reported a serious adverse event, with significantly more patients being affected in the nab-Paclitaxel weekly arm (31.9% vs 24.7%, respectively, p=0.031), the effect being driven by non-hematological serious adverse events (26.8% vs 18.8%, respectively, p=0.010). Adverse events of special interest were relatively rare with a total of 29 (3.8%) of patients being affected with no significant difference between nab-Paclitaxel arms.

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

Table Summary of Adverse Events, denosumab randomization (safety set, N=768)

Predefined AEs*	Denosumab N=377 N(%)	No denosumab N=391 N(%)	Overall N=768 N(%)	p-value
Any AE, any grade	377 (100)	391 (100)	768 (100)	n.a.
Any AE, high-grade	279 (74.0)	306 (78.3)	585 (76.2)	0.176
Hematological AE, any grade	374 (99.2)	390 (99.7)	764 (99.5)	0.365
Hematological AE, high-grade	245 (65.0)	274 (70.1)	519 (67.6)	0.143
Non-hematological AE, any grade	376 (99.7)	391 (100)	767 (99.9)	0.491
Non-hematological AE, high-grade	114 (30.2)	109 (27.9)	223 (29.0)	0.476
SAE	108 (28.6)	110 (28.1)	218 (28.4)	0.936
Hematological SAE	31 (8.2)	44 (11.3)	75 (9.8)	0.181
Non-hematological SAE	89 (23.6)	87 (22.3)	176 (22.9)	0.668
AESI	15 (4.0)	14 (3.6)	29 (3.8)	0.851

Table Summary of Adverse Events, nab-Paclitaxel randomization (safety set, N=768)

Predefined AEs*	nP weekly N=395 N(%)	nP d1,8 q22 N=373 N(%)	Overall N=768 N(%)	p-value
Any AE, any grade	395 (100)	373 (100)	768 (100)	n.a.
Any AE, high-grade	312 (79.0)	273 (73.2)	585 (76.2)	0.063
Hematological AE, any grade	393 (99.5)	371 (99.5)	764 (99.5)	1.000
Hematological AE, high-grade	267 (67.6)	252 (67.6)	519 (67.6)	1.000
Non-hematological AE, any grade	395 (100)	372 (99.7)	767 (99.9)	0.486
Non-hematological AE, high-grade	133 (33.7)	90 (24.1)	223 (29.0)	0.004
SAE	126 (31.9)	92 (24.7)	218 (28.4)	0.031
Hematological SAE	40 (10.1)	35 (9.4)	75 (9.8)	0.808
Non-hematological SAE	106 (26.8)	70 (18.8)	176 (22.9)	0.010
AESI	17 (4.3)	12 (3.2)	29 (3.8)	0.455

Within breast cancer subtypes defined according to treatment added to chemotherapy backbone, no differences between groups were found in the denosumab randomization for any of the predefined adverse event categories. Among patients with HER2-/HR+ tumors, high grade adverse events were more common in the nab-Paclitaxel weekly arm compared to the nab-Paclitaxel d1,8 q22 arm (72.4% vs. 60.7%, p=0.038), while none of the other adverse event categories were significantly different. For the TNBC subtype, significantly more patients in the nab-Paclitaxel weekly arm were reported to have high-grade non-

hematological adverse events (38.3% vs. 24.5%, p=0.011) and non-hematological SAEs (35.9% vs. 23.1%, p=0.014), respectively. There were no differences between nab-Paclitaxel groups for patients with HER2+ tumors for any of the predefined adverse event categories.

There was one death during study treatment in the group treated with denosumab and nab-paclitaxel d1,8 q22 due to an unknown reason (cycle 4). The event was initially considered as not assessable by the investigator. Thereafter, it was rated as possibly related to nab-paclitaxel treatment.

Safety Conclusions

All patients received a median of 6 denosumab injections. For the overall population, the addition of denosumab did not significantly impact the median treatment duration of nab-Paclitaxel which was 8.0 (range 2.0-12.0) weeks in patients treated with denosumab vs 9.0 (range 2.0-12.0) weeks in patients treated without denosumab (p=0.739). The median duration of nab-Paclitaxel was only significantly different in the HER2-/HR+ subtype (defined according to treatment added to chemotherapy backbone. Here, patients treated with denosumab received a median of 8.0 (range 4.0-12.0) weeks nab-Paclitaxel and without denosumab 11.0 (range 3.0-12.0) weeks (p=0.004). To note, no statistical comparison of different number of weeks between arms was performed in the nab-Paclitaxel randomization by design.

Interestingly, neither the addition of denosumab nor the regimen of nab-Paclitaxel significantly affected the median treatment duration of carboplatin as well as the number of cycles of EC. The median treatment duration of carboplatin in the overall population (TNBC patients) was 12.0 weeks, the median number of cycles for all patients that started with EC, was 4 cycles.

Adverse events were the main reasons to discontinue nab-Paclitaxel in both nab-Paclitaxel-arms. Significantly more patients discontinued nab-Paclitaxel weekly vs nab-Paclitaxel d1,8 q22 (20.5% vs. 6.2%, p<0.001). However, there was no difference between nab-Paclitaxel weekly and nab-Paclitaxel d1,8 q22 in terms of discontinuation of EC (7.7% vs 5.9%; p=0.377). Again, the addition of denosumab did not significantly affect the treatment discontinuations of nab-paclitaxel or EC and among those patients that started denosumab, no difference was observed in terms of denosumab discontinuation between both nab-Paclitaxel arms.

Likewise, denosumab did not impact dose delays of all study chemotherapies (any reason) in the overall safety population, but there was a significant effect of the two different treatment regimen of nab-Paclitaxel on delays which could be shown for delays of nab-Paclitaxel, carboplatin, EC as well as combined for any chemotherapy. nab-Paclitaxel doses had to be delayed significantly more often in the nab-Paclitaxel weekly arm (nP weekly: 76.2%, nP d1,8 q22: 56.0%, p<0.001) in the overall safety population. Among the reasons for dose delays of nab-Paclitaxel, dose delays due to organizational reasons (nP weekly: 52.4%, nP d1,8 q22: 35.9%, p<0.001), due to hematological toxicity (nP weekly: 26.3%, nP d1,8 q22: 18.2%, p=0.007), due to other non-hematological toxicity (nP weekly: 17.7%, nP d1,8 q22: 6.4%, p<0.001), and due to adverse events not related to the study medication (nP weekly: 11.4%, nP d1,8 q22: 4.8%, p<0.001) were all observed significantly more often in the nab-Paclitaxel weekly arm. Likewise, doses of carboplatin had to be delayed due to any reason significantly more often in the nab-Paclitaxel weekly arm for the overall safety population (nP weekly: 86.2%, nP d1,8 q22: 75.5%, p=0.020) in the overall safety population.

In addition, doses of EC had to be reduced significantly more often in the nab-Paclitaxel weekly arm due to any reason in the overall safety population (nP weekly: 23.6%, nP d1,8 q22: 15.7%, p=0.009) as well in TNBC (nab-Paclitaxel weekly: 36.7%, nab-Paclitaxel d1,8 q22: 23.0%, p=0.014).

Treatment interruptions of denosumab were rare and did not differ significantly between nab-Paclitaxel arms. In addition, denosumab did not affect the treatment interruptions of nab-Paclitaxel. Infusions of nab-

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

Paclitaxel were skipped significantly more often in the nab-Paclitaxel weekly arm due to any reason (nab-Paclitaxel weekly: 7.3%, nab-Paclitaxel d1,8 q22: 2.9%, p=0.009), and mostly due to other non-hematological toxicity (nab-Paclitaxel weekly: 3.0%, nab-Paclitaxel d1,8 q22: 0.5%, p=0.013). However, treatment interruptions of EC and of carboplatin did not differ significantly between the denosumab or nab-Paclitaxel arms in the overall safety population.

In the overall safety population, all patients experienced at least one AE of any grade during study treatment. Regarding the both randomizations, only high-grade non-hematological adverse events were significantly more frequent in the nab-Paclitaxel weekly arm compared to the nab-Paclitaxel d1,8 q22 arm (33.7% vs 24.1%, respectively, p=0.004).

Within both arms of the denosumab randomization, anaemia (denosumab: 94.7%, no denosumab: 96.9%), leukopenia (denosumab: 94.2%, no denosumab: 96.2%), and neutropenia (denosumab: 89.9%, no denosumab: 90.5%) of any grade and high grade neutropenia (denosumab: 60.7%, no denosumab: 64.7%) were the most frequent hematological adverse events in the overall safety population- except febrile neutropenia (denosumab: 4.5%, no denosumab: 8.2%, p=0.039) there were no significant differences between the two arms in terms of hematological adverse events.

The most frequent predefined non-hematological AEs of any grade were alopecia (denosumab: 86.7%, no denosumab: 86.2%), fatigue (denosumab: 71.6%, no denosumab: 69.8%), nausea (denosumab: 59.7%, no denosumab: 60.9%), and peripheral sensory neuropathy (denosumab: 59.9%, no denosumab: 62.7%). Higher frequencies in the denosumab arm were found for any grade hypocalcaemia (denosumab: 51.2%, no denosumab: 28.6%, p<0.001), any grade myalgia (denosumab: 16.7%, no denosumab: 11.0%, p=0.028), and any grade other adverse events reported as free-text (denosumab: 19.1%, no denosumab: 13.6%, p=0.040). Relevant differences of free-text adverse events within the denosumab randomization with higher frequencies in the denosumab arm were found for any grade mucosal inflammation (denosumab: 25.5%, no denosumab: 17.9%, p=0.011), high grade mucosal inflammation (denosumab: 1.9%, no denosumab: 0.3%, p=0.035), and high grade blood calcium increased (denosumab: 3.7%, no denosumab: 1.3%, p=0.036). Any grade other respiratory, thoracic and mediastinal disorders were significantly more common in the no denosumab arm (denosumab: 13.3%, no denosumab: 18.9%, p=0.039).

Regarding the nab-Paclitaxel randomization, anaemia (nP weekly: 96.7%, nPd1,8 q22: 94.9%), leukopenia (nP weekly: 96.2%, nP d1,8 q22: 94.1%), and neutropenia (nP weekly: 91.4%, nP d1,8 q22: 89.0%) of any grade and high grade neutropenia (nP weekly: 63.8%, nP d1,8 q22: 61.7%) were the most frequent hematological adverse events in the overall safety population. None of the hematological adverse events of any or high grade were significantly different between both nab-Paclitaxel arms.

The most frequent non-hematological AEs of any grade were alopecia (nP weekly: 87.3%, nP d1,8 q22: 85.5%), fatigue (nP weekly: 73.9%, nP d1,8 q22: 67.3%, p=0.047), peripheral sensory neuropathy (nP weekly: 74.9%, nP d1,8 q22: 46.9%, p<0.001), and nausea (nP weekly: 56.2%, nP d1,8 q22: 64.6%). Relevant differences in the category of non-hematological AEs with higher frequencies in the nab-Paclitaxel weekly arm were additionally found for any grade decreased appetite (nP weekly: 15.4%, nP d1,8 q22: 10.2%, p=0.031), diarrhoea (nP weekly: 41.5%, nP d1,8 q22: 33.2%, p=0.021), arthralgia (nP weekly: 25.3%, nP d1,8 q22: 19.0%, p=0.038), epistaxis (nP weekly: 26.8%, nP d1,8 q22: 13.9%, p<0.001), palmar-plantar erythrodysaesthesia syndrome (nP weekly: 8.6%, nP d1,8 q22: 3.5%, p=0.004), pyrexia (nP weekly: 19.2%, nP d1,8 q22: 11.8%, p=0.005), pneumonia (nP weekly: 3.0%, nP d1,8 q22: 0.5%, p=0.013), high grade peripheral sensory neuropathy (nP weekly: 5.3%, nP d1,8 q22: 1.1%, p<0.001), and other adverse events reported as free-text (nP weekly: 94.4%, nP d1,8 q22: 89.8%, p=0.022).

Relevant differences for free-text adverse events with higher frequencies in the nab-Paclitaxel weekly arm were found for any grade insomnia (nP weekly: 10.6%, nP d1,8 q22: 6.2%, p=0.028), other psychiatric

disorders (nP weekly: 14.4%, nP d1,8 q22: 9.1%, p=0.025), other eye disorders (nP weekly: 21.3%, nP d1,8 q22: 11.0%, p<0.001), abdominal pain (nP weekly: 7.6%, nP d1,8 q22: 2.4%, p=0.003), stomatitis (nP weekly: 13.9%, nP d1,8 q22: 9.1%, p=0.042), dry skin (nP weekly: 11.9%, nP d1,8 q22: 5.6%, p=0.002), erythema (nP 7.8%, nP d1,8 q22: 4.0%, p=0.032), nail discolouration (nP weekly: 10.9%, nP d1,8 q22: 5.1%, p=0.003), nail disorder (nP weekly: 7.6%, nP d1,8 q22: 3.2%, p=0.010), rash (nP weekly: 24.6%, nP d1,8 q22: 13.4%, p<0.001), other skin and subcutaneous tissue disorders (nP weekly: 43.8%, nP d1,8 q22: 26.5%, p<0.001), and peripheral oedema (nP weekly: 8.6%, nP d1,8 q22: 4.3%, p=0.019). Only nausea of any grade (nP weekly: 56.2%, nP d1,8 q22: 64.6%, p=0.018), any grade other reproductive system and breast disorders (nP weekly: 4.1%, nP d1,8 q22: 10.2%, p=0.001) and any grade increased blood calcium (nP weekly: 3.8%, nP d1,8 q22: 7.2%, p=0.039) were significantly more common in the nab-Paclitaxel d1,8 q22 arm.

Peripheral sensory neuropathy of grade 2-4 (nP weekly: 30.4%, nP d1,8 q22: 8.3%, p<0.001) and grade 3-4 (nP weekly: 5.3%, nP d1,8 q22: 1.1%, p<0.001) was reported significantly more often in the nab-Paclitaxel weekly arm. The onset of grade 2-4 and grade 3-4 peripheral sensory neuropathy was predominantly during cycle 4. Recovery of grade 2-4 peripheral sensory neuropathy to grade 1 until end of treatment was comparable between nab-Paclitaxel arms (nP weekly: 58.3%, nP d1,8 q22: 64.5%, p=0.682). Median time for grade 2-4 peripheral sensory neuropathy to resolve to grade 1 was 10.3 weeks for nab-Paclitaxel weekly and 12.4 weeks for nab-Paclitaxel d1,8 q22. Similarly, recovery of grade 3-4 peripheral sensory neuropathy to grade 1 until end of treatment was comparable between nab-Paclitaxel arms (nP: 28.6%, nP d1,8 q22: 25.0%, p=1.000). Median time for grade 3-4 peripheral sensory neuropathy to resolve to grade 1 was not reached.

There was one death during study treatment in the group treated with denosumab and nab-paclitaxel d1,8 q22 due to an unknown reason (cycle 4). The event was initially considered as not assessable by the investigator. Thereafter, it was rated as possibly related to nab-paclitaxel treatment.

Predefined adverse events of special interest were relatively rare with a total of 29 (3.8%) of patients being affected.

A total of 359 SAEs for 218 patients were reported, with significantly more patients being affected in the nab-Paclitaxel weekly arm (31.9% vs 24.7%, respectively, p=0.031), with the effect being driven by non-hematological serious adverse events (26.8% vs 18.8%, respectively, p=0.010). The overall incidence of SAEs differs between the treatment groups, only marginally between denosumab groups (denosumab: 178 SAEs, no denosumab: 181 SAEs), but to a greater extent between nab-Paclitaxel groups (nab-Paclitaxel weekly: 220 SAEs, nab-Paclitaxel d1,8 q22: 139 SAEs).

In the denosumab randomization, the most prominent differences between the treatment groups with higher frequencies in the denosumab arm were observed for SOCs respiratory, thoracic and mediastinal disorders (denosumab: 11 SAEs, no denosumab: 3 SAEs), and general disorders and administration site conditions (denosumab: 48 SAEs, no denosumab: 36 SAEs), and with higher frequencies in the no denosumab arm for SOCs infections and infestations (denosumab: 24 SAEs, no denosumab: 33 SAEs), gastrointestinal disorders (denosumab: 12 SAEs, no denosumab: 19 SAEs), cardiac disorders (denosumab: 1 SAE, no denosumab: 8 SAEs), and nervous system disorders (denosumab: 1 SAE, no denosumab: 5 SAEs).

In the nab-Paclitaxel randomization, the most prominent differences between the treatment groups with higher frequencies in the nab-Paclitaxel weekly arm were observed for SOCs infections and infestations (nP weekly: 35 SAEs, nP d1,8 q22: 22 SAEs), blood and the lymphatic system disorders (nPweekly: 60 SAEs, nP d1,8 q22: 48 SAEs), gastrointestinal disorders (nP weekly: 21 SAEs, nP d1,8 q22: 10 SAEs), general disorders and administration site conditions (nP weekly: 56 SAEs, nP d1,8 q22: 28 SAEs), and injury, poisoning and procedural complications (nP weekly: 7 SAEs, nP d1,8 q22: 0 SAEs), and with higher frequencies in the no denosumab arm for SOCs cardiac disorders (nP weekly: 3 SAEs, nP d1,8 q22: 6 SAEs).

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

In conclusion, the safety profile for denosumab and the two different nab-Paclitaxel regimens observed in the GeparX trial is in line with observations derived from other trials investigating different nab-Pacitaxel regimens or denosumab. No new safety concerns have emerged from the addition of denusumab to neoadjuvant chemotherapy. After assessment of all safety data, the overall risk-benefit ratio of the GeparX study remains unchanged and the use of both nab-Paclitaxel regimens as well as the neoadjuvant use of denosumab appears feasible in this patient population.

ABP 980 (HER2+) substudy results:

In the subgroup of 153 patients (152 started treatment) with HER2-positive tumors that received neoadjuvant treatment with ABP 980 and pertuzumab, the pCR (ypT0 ypN0) rate was 54.9%, with a non-significant difference between nab-Paclitaxel arms (nab-Paclitaxel weekly 57.9%, nab-Paclitaxel d1,8 q22 51.9%, p=0.289). For patients with HER2-positive tumors treated with trastuzumab and pertuzumab in addition to nab-paclitaxel weekly in the GeparSepto trial, a pCR rate of 62% was observed. There was no significant difference in pCR rates between denosumab arms in patients with HER2-positive tumors that received neoadjuvant treatment with ABP 980 and pertuzumab (denosumab 55.8%, no denosumab 53.9%, p=0.821).

pCR rates (ypT0 ypN0) in HER2+ patients treated with ABP 980 were also not significantly different when assessed according to HR status: HR-negative (N=48) denosumab 88.0%, no denosumab 78.3%, p=0.605, and nab-Paclitaxel weekly 88.9%, nab-Paclitaxel d1,8 q22 80.0%, p=0.689; HR-positive (N=105) denosumab 40.4%, no denosumab 43.4%, p=0.909, and nab-Paclitaxel weekly 48.3%, nab-Paclitaxel d1,8 q22 34.0%, p=0.204.

Similarly, no significant differences were found in both randomizations for other pCR definitions for the HER2+ cohort: pCR (ypT0/is ypN0) rate was 64.7% (denosumab 64.9%, no denosumab 64.5%, p=1.000; nab-Paclitaxel weekly 67.1%, nab-Paclitaxel d1,8 q22 62.3%, p=0.654), pCR (ypT0 ypN0/+) rate was 58.8% (denosumab 58.4%, no denosumab 59.2%, p=1.000; nab-Paclitaxel weekly 61.8%, nab-Paclitaxel d1,8 q22 55.8%, p=0.556), pCR (ypT0/is ypN0/+) rate was 70.6% (denosumab 70.1%, no denosumab 71.1%, p=1.000; nab-Paclitaxel weekly 75.0%, nab-Paclitaxel d1,8 q22 66.2%, p=0.311), and pCR (ypTany ypN0) rate was 85.0% (denosumab 85.7%, no denosumab 84.2%, p=0.973; nab-Paclitaxel weekly 81.6%, nab-Paclitaxel d1,8 q22 88.3%, p=0.348).

There were no significant differences in overall clinical (imaging) response rate (ORR, defined as complete or partial response) of the breast before surgery in HER2-positive patients between arms in any of the two randomizations (ORR denosumab 90.9%, no denosumab 97.4%, p=0.176; nab-Paclitaxel weekly: 93.4%, nab-Paclitaxel d1,8 q22: 94.8%, p=0.984). Breast conservation rates in the HER2+ cohort were also similar between arms in the two randomizations (denosumab 73.7%, no denosumab 80.0%, p=0.467; nab-Paclitaxel weekly: 77.6%, nab-Paclitaxel d1,8 q22: 76.8%, p=0.964).

One patient in the subgroup of 153 patients with HER2-positive tumors did not start treatment. A total of 18 patients (11.8%) discontinued anti-HER2 treatment before chemotherapy, of those 7 discontinued both ABP 980 and pertuzumab, 8 discontinued ABP 980 but not pertuzumab, and 3 discontinued pertuzumab but not ABP 980. Discontinuations of anti-HER2 treatment were not significantly different between denosumab and nab-Paclitaxel arms.

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

Table: Summary of Adverse Events, HER2+ subtype, denosumab randomization (N=152)

Predefined AEs	Denosumab N=75 N(%)	No denosumab N=77 N(%)	Overall N=152 N(%)	p-value
Any AE, any grade	75 (100)	77 (100)	152 (100)	n.a.
Any AE, high-grade	51 (68.0)	53 (68.8)	104 (68.4)	1.000
Hematological AE, any grade	75 (100)	77 (100)	152 (100)	n.a.
Hematological AE, high-grade	44 (58.7)	45 (58.4)	89 (58.6)	1.000
Non-hematological AE, any grade	75 (100)	77 (100)	152 (100)	n.a.
Non-hematological AE, high-grade	25 (33.3)	23 (29.9)	48 (31.6)	0.728
SAE	19 (25.3)	20 (26.0)	39 (25.7)	1.000
Hematological SAE	2 (2.7)	4 (5.2)	6 (3.9)	0.681
Non-hematological SAE	18 (24.0)	17 (22.1)	35 (23.0)	0.848
AESI	11 (14.7)	10 (13.0)	21 (13.8)	0.817

Table: Summary of Adverse Events, HER2+ subtype, nab-Paclitaxel randomization (N=152)

Predefined AEs	nP weekly N=76 N(%)	nP d1,8 q22 N=76 N(%)	Overall N=152 N(%)	p-value
Any AE, any grade	76 (100)	76 (100)	152 (100)	n.a.
Any AE, high-grade	51 (67.1)	53 (69.7)	104 (68.4)	0.862
Hematological AE, any grade	76 (100)	76 (100)	152 (100)	n.a.
Hematological AE, high-grade	44 (57.9)	45 (59.2)	89 (58.6)	1.000
Non-hematological AE, any grade	76 (100)	76 (100)	152 (100)	n.a.
Non-hematological AE, high-grade	24 (31.6)	24 (31.6)	48 (31.6)	1.000
SAE	23 (30.3)	16 (21.1)	39 (25.7)	0.265
Hematological SAE	2 (2.6)	4 (5.3)	6 (3.9)	0.681
Non-hematological SAE	21 (27.6)	14 (18.4)	35 (23.0)	0.248
AESI	13 (17.1)	8 (10.5)	21 (13.8)	0.347

There were no differences between denosumab arms or nab-Paclitaxel arms for patients with HER2+ tumors for any of the predefined adverse event categories.

None of the predefined AEs of special interest for HER2-positive patients treated with ABP 980 (pneumonia, other pulmonary toxicity, cough, pneumonitis, cardiac failure (NYHA), hypersensitivity, infusion related reaction, and high grade infection other than pneumonia) were observed in more than 5% of patients and there were no differences between arms.

The incidence of any grade diarrhoea was 75.0%, of grade 3-4 diarrhoea 3.9% in the HER2+ cohort with no

significant differences between denosumab arms. Any grade diarrhoea was observed significantly more often in the nab-Paclitaxel weekly arm (nab-Paclitaxel weekly 82.9%, nab-Paclitaxel d1,8 q22 67.1%, p=0.0.039). Compared to the overall cohort (any grade diarrhoea: 37.5%, grade 3-4 diarrhoea : 2.0%) the incidence of diarrhoea was higher in patients with HER2+ tumors. Cardiovascular events in terms of cardiac failure (NYHA) were not observed in patients with HER2+ tumors, while in the overall cohort one patient was affected.

In patients with HER2+ tumors under EC, significant differences among the predefined hematological or non-hematological adverse events were found for any grade dyspnea (denosumab: 13.9%, no denosumab: 4.1%, p=0.046) and any grade hypocalcaemia (denosumab: 41.7%, no denosumab: 16.4%, p<0.001) which were both more common in the denosumab arm. Within the nab-Paclitaxel randomization, significantly more HER2+ patients in the nab-Paclitaxel weekly arm had any grade peripheral sensory neuropathy (nab-Paclitaxel weekly: 72.2%, nab-Paclitaxel d1,8 q22: 37.0%, p<0.001) under EC treatment.

Analysis of long-term outcome (LRRFS, DDFS, iDFS, EFS, and OS) for the HER2+ cohort will be reported later with long-term outcome of the overall cohort.

Disseminated tumor cells (DTC) substudy results:

A total of 167 patients were analyzed in the DTC substudy at baseline. 43/167 patients (25.7%) were DTC-positive and 41 of those were available for re-analysis of DTCs after neoadjuvant chemotherapy ± denosumab. DTC eradication was observed in 77.8% after neoadjuvant chemotherapy + denosumab and in 69.6% after neoadjuvant chemotherapy alone (p=0.726). Due to the limited number of patients eligible for DTC-re-analysis after neoadjuvant chemotherapy, a subtype specific analysis for the effect of denosumab was not possible.

Overall, 60/167 patients (35.9%) treated with neoadjuvant chemotherapy ± denosumab had a pathological complete response (55.4% in TNBC, 43.3% in HER2+, 15.3% in HR+/HER2-). There was no significant association between pCR and the presence of DTCs at baseline (37.1% DTC-negative vs 32.6% positive, p=0.713) or between pCR and the eradication of DTCs after neoadjuvant chemotherapy ± denosumab (36.7% vs 27.3%, p=0.719). Notably, in TNBC, we observed a tendency that DTC-positivity at baseline or DTC-persistence after neoadjuvant chemotherapy could be associated with reduced pCR rate: 7/17 (41.2%) in DTC-positive vs. 29/48 (60.4%) in DTC-negative patients, p=0.256; 1/4 (25%) in DTC-persistent patients vs. 6/12 (50.0%) in DTC-eradicated patients, p=0.585).

OVERALL CONCLUSIONS:

The prospectively randomized phase IIb neoadjuvant GeparX study aimed to investigate the addition of RANK-ligand inhibition with denosumab as well as two different nab-paclitaxel schedules in terms of toxicity and anti-cancer efficacy. Both co-primary objectives were addressed for patients with early high-risk breast cancer with the endpoint pCR (ypT0 ypN0) in a 2x2 factorial design.

There was no significant difference in pCR rates for patients treated preoperatively with or without denosumab in addition to nab-paclitaxel schedules followed by EC 2- or 3-weekly (41.0% vs 42.8%, p=0.582). However, GeparX study demonstrated a significant (to the pre-defined significance level of α=0.1) increase in pCR rates with weekly nab-Paclitaxel vs nab-Paclitaxel d1,8 q22 with an absolute and clinically meaningful difference of 5.9% (44.9% vs 39.0%, p=0.062). This effect was especially seen in patients with TNBC which received also carboplatin AUC2 weekly in addition to nab-Paclitaxel schedules. Here, the pCR rate was 60.4% with nab-Paclitaxel weekly vs 50.0% with nab-Paclitaxel d1,8 q22 (p=0.056) whereas in the hormone receptor and HER2-positive group there were no significant differences between both nab-Paclitaxel

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

schedules.

In addition, the pCR rate was statistically significantly higher with nab-Paclitaxel weekly followed by EC 2-weekly (nab-Paclitaxel weekly: 46.9%, nab-Paclitaxel d1,8 q22: 36.7%, p=0.038), and with nab-Paclitaxel weekly and in combination with denosumab treatment (nab-Paclitaxel weekly: 48.2%, nab-Paclitaxel d1,8 q22: 33.8%, p=0.027) for the whole study population; however, the test for interaction between denosumab and nab-paclitaxel randomization was negative (p=0.275) in the multivariate model. It should be also noted that there was no adjustment for multiple comparisons and results of the subgroup analysis have to be interpreted with caution.

In the subgroup of patients with HER2-positive tumors that received neoadjuvant treatment with the biosimilar ABP 980 and pertuzumab, the pCR (ypT0 ypN0) rate was 54.9%. No significant differences were found for the denosumab randomisation and nab-Palitaxel randomisation as well as when pCR rate was assessed according to HR status or for other pCR definitions. The pCR rate for patients treated with the biosimilar ABP980 in combination with pertuzumab was 57. 9% with nab-Paclitaxel weekly. Here, the pCR rate was similar to the pCR rate of 62% decribed for patients with HER2-positive tumors and treatment with trastuzumab and pertuzumab in addition to nab-paclitaxel weekly in the GeparSepto trial (Untch et al. Lancet Oncol 2016). This supports the co-administration of the biosimilar ABP980 with pertuzumab.

Overall, the pCR Rates of the GeparX study were generally higher than observations derived from previous neoadjuvant studies investigating nab-Paclitaxel as part of anthracycline-taxane based neoadjuvant treatment. The GeparSepto study, for example, showed a lower pCR rate of 38% with nab-Paclitaxel weekly followed by EC 3-weekly for the overall study population and 48% for patients with TNBC (Untch et al. Lancet Oncol 2016).This could be explained by the fact, that according to protocol GeparX study patients received optimized chemotherapy with EC every 2 or 3 weeks (investigator´s decision) and all TNBC patients received carboplatin AUC2 weekly in addition to nab-Paclitaxel regime based on the results from GeparSixto study and CALGB 40603 study (von Minckwitz et al. Lancet Oncol 2014; Sikov et al, J Clin Oncol 2015).

Additionally, the primary endpoint pCR was analyzed in the subgroups according to RANK high vs low expression for both randomizations. There was no difference according to RANK expression, neither between the denosumab, nor between the nab-paclitaxel arms. Likewise, there were no significant differences concerning clinical response in the breast, breast conservation rate as well as axillary surgery surgery between arms in any of the two randomizations. Despite preclinical evidence (Dougall et al. Clin Cancer Res 2012) and analyses of breast cancer samples (Pfitzner et al. Breast Cancer Res Treat 2014) suggesting that RANKL inhibition might improve the outcome of neoadjuvant chemotherapy, an improvement of outcome parameters by the addition of denosumab could not be shown. Although the adjuvant ABCSG- 18 study showed reduced clinical factures, improved bone health as well as beneficial effects on longterm survival for patients with early HR-positive breast (Gnant et al. Lancet 2015), GeparX could not demonstrate a anti-cancer effect of denosumab on pCR rate for high-risk early breast cancer patients treated with neoadjuvant chemotherapy.

Meanwhile, results of the D-Care study which evaluated Denosumab combined with standard-of-care adjuvant or neoadjuvant systemic therapy in women with early stage high-risk breast cancer became available. Also here, denosumab did not improve disease-related outcomes for women with high-risk early breast cancer (Coleman et al, Lancet Oncol 2020).

In the overall safety population, all patients experienced at least one AE of any grade during study treatment. Regarding the both randomizations, only high-grade non-hematological adverse events were significantly more frequent in the nab-Paclitaxel weekly arm compared to the nab-Paclitaxel d1,8 q22 arm (33.7% vs 24.1%, respectively, p=0.004). Inter alia, relevant differences were described for fatigue (nP weekly: 73.9%, nP d1,8 q22: 67.3%, p=0.047), peripheral sensory neuropathy (nP weekly: 74.9%, nP d1,8

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

q22: 46.9%, p<0.001), diarrhoea (nP weekly: 41.5%, nP d1,8 q22: 33.2%, p=0.021), arthralgia (nP weekly: 25.3%, nP d1,8 q22: 19.0%, p=0.038), and epistaxis (nP weekly: 26.8%, nP d1,8 q22: 13.9%, p<0.001).

As expected, the incidence of diarrhoea was higher in patients with HER2+ tumors (any grade diarrhoea: 75.0%, grade 3-4 diarrhoea 3.9%) compared to the overall cohort (any grade diarrhoea: 37.5%, grade 3-4 diarrhoea: 2.0%). Cardiovascular events in terms of cardiac failure (NYHA) were not observed in patients with HER2+ tumors, while in the overall cohort one patient was affected.

Peripheral sensory neuropathy of grade 3-4 (nP weekly: 5.3%, nP d1,8 q22: 1.1%, p<0.001) was reported significantly more often in the nab-Paclitaxel weekly arm with a predominately onset during cycle 4. Interestingly, the percentage of patients with recovery of grade 3-4 peripheral sensory neuropathy to grade 1 at end of treatment was comparable between both nab-Paclitaxel schedules (nP: 28.6%, nP d1,8 q22: 25.0%).

Interestingly, neither the addition of denosumab nor the regimen of nab-Paclitaxel significantly affected the median number (4) of cycles of EC (whole study population) or the median number of administrations of carboplatin (onlyTNBC patients). Treatment discontinuations occurred more frequently in the nab-Paclitaxel weekly (20.5% vs. 6.2%, p<0.001) arm mainly due to adverse events.

A total of 359 SAEs for 218 patients were reported, with significantly more patients being affected in the nab-Paclitaxel weekly arm (31.9% vs 24.7%, respectively, p=0.031), with the effect being driven by non-hematological serious adverse events (26.8% vs 18.8%, respectively, p=0.010). There was one death of unknown reason possibly related to nab-paclitaxel during study treatment in the group treated with denosumab and nab-paclitaxel d1,8 q22 . Special side effects known to be associated with denosumab were relatively rare. Hypocalcaemia of any grade was significantly higher in the denosumab arm (denosumab: 51.2%, no denosumab: 28.6%, p<0.001). There was only one osteonecrosis of the jaw in a patient treated with denosumab and nab-Paclitaxel d1,8 q22.

The safety profile for denosumab and the two different nab-Paclitaxel regimens observed in the GeparX trial was in line with observations derived from other trials investigating Denosumab (Gnant et al. Lancet 2015; Coleman et al. Lancet Oncol 2020) or nab-Paclitaxel (Untch et al. Lancet Oncol 2016, Furlanetto et al. Breast Cancer Res Treat 2017) in early brast cancer. According to protocol patients randomized to nab-Paclitaxel weekly were treated with 4 additional administrations of nab-Paclitaxel without any breaks. Therefore, it is not surprising that the nab-Paclitaxel d1,8 q22 regime regimen has a better toxicity profile.

The GeparX study has strengths and limitations. It is a randomized phase IIb study with a large biomarker program. With regard to different breast cancer subtypes the chemotherapy design is straightforward and mirrors standard of care. Two important questions were evaluated with one endpoint. All subjects were randomized according to central pathology assessment and were at high-risk. Unfortunately, GeparX will not collect further data on peripheral sensory neuropathy and is not powered to demonstrate further statistically significant differences in longterm survival outcomes.

In conclusion, the addition of denosumab to neoadjuvant chemotherapy did not statistically significantly increase the pCR rate in patients with early breast cancer. Nab-paclitaxel 125mg/m² weekly resulted in a significantly higher pCR rate than given d1,8 q22 in the whole study population. The remarkable pCR rate of 60.4% in patients with TNBC supports the use of optimized neoadjuvant chemotherapy with nab-Paclitaxel 125mg/m² weekly plus carboplatin in combination with EC. The safety profile for denosumab and the two different nab-Paclitaxel regimens observed in the GeparX trial was in line with observations derived from other trials. Therefore, the use of nab-Paclitaxel regimens as well as the neoadjuvant use of denosumab appears feasible in this breast cancer patient population. Long-term follow-up as well as translational research is ongoing.

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

Analysis of long-term outcome (LRRFS, DDFS, iDFS, EFS, and OS) will be reported later with sufficient follow-up. Further correlative and translational science objectives (comparison of RANK/L and Ki-67 from baseline to surgery, correlation of response after the first two cycles of treatment with pCR, as well as quality of life) have not yet been analysed and will be reported later.

Date of the Report:

December 17, 2020

Annex 1

Amendment to Protocol

There were three substantial Amendments to the protocol of GeparX pertaining to the following contents:

Amendment 1:
Inclusion of a trastuzumab biosimilar replacing Herceptin® (and thus opening the study for patients with HER2-positive tumor), minor adjustments to the protocol and deletion of the PET-CT substudy.

Amendment 2:
Change of co-ordinating Investigator and adjustments in patient informed consent required due to several updates to the reference document for the investigational medicinal product Denosumab.

Amendment 3:
Clarification of end of study and timeframe from end of therapy until surgery.
Several reformulations and additions in patient informed consent, especially for the marketing authorization of the trastuzumab biosimilar.