CLINICAL STUDY REPORT

A randomized phase III trial comparing two dose-dense, dose-intensified approaches (ETC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer

EudraCT no: 2014-000619-14

Indication:	Early breast cancer
Phase:	III
Study Protocol:	GBG 84 Protocol (August 8th, 2014) Protocol Amendment 1 (November 15th, 2015)
Investigational Products:	Carboplatin Doxorubicinhydrochloride (Myocet®) Pertuzumab (Perjeta®) Ferric Carboxymaltose (Ferinject®) Epirubicin Cyclophosphamide Trastuzumab (Herceptin®) Paclitaxel
Clinical Study Report Version:	Version 2 (July 19th, 2019)
First Patient Enrolled:	December 1st, 2014
Last Patient Completed:	December 4th, 2016
Co-ordinating Investigator:	Prof. Dr. Andreas Schneeweiss Universitätsfrauenklinik Heidelberg D-69120 Heidelberg, Im Neuenheimer Feld 460

1. SYNOPSIS

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

Title of Study:

A randomized phase III trial comparing two dose-dense, dose-intensified approaches (ETC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto)

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

Publication (reference):

Schneeweiss A, Moebus V, Tesch H, Hanusch C, Denkert C, Luebbe K et al. A randomised phase III trial comparing two dose-dense, dose-intensified approaches (EPC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto). J Clin Oncol 35, 2017 (suppl; abstr 518)

Full publication in preparation.

Studied Period (years):

Date of the first patient enrolled: 01-Dec-2014
Date of the last patient completed: 06-Dec-2016 (last patient had surgery)

Phase of Development:

Phase III

Objectives:

Primary Objective of the Main Study:

In the overall study, the primary objective was to compare the pathological complete response (pCR=ypT0/is ypN0) rates of neoadjuvant treatment with sequential, dose-dense, dose-intensified ETC(+HP [T) vs. weekly PM(Cb)(+HP) in patients with high-risk operable or locally advanced breast cancer.

Secondary Objectives of the Main Study:

In the overall study the secondary objectives were to:

- Assess the pCR rates per arm separately for the stratified subpopulations.
- Determine the rates of ypT0 ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT(any) ypN0; and the residual cancer burden (RCB) score.
- 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.
- Determine the breast conservation rate after each treatment.
- Assess the toxicity and compliance including incidence of febrile neutropenia, cardiac dysfunction/failure and frequency of dose delays and reductions per arm and subtype.
- Determine loco-regional invasive recurrence free survival (LRRFS), distant-disease-free survival (DDFS), invasive disease-free survival (IDFS), and overall survival (OS) in both arms and according to stratified subpopulations.
- Assess regional recurrence free survival (RRFS) in patients with initial node-positive axilla converted to negative (ypN0) at surgery and treated with sentinel node biopsy alone.
- Determine the pCR rate and local recurrence free survival (LRFS) in patients with a clinical complete response (cCR) and a negative core biopsy before surgery.

Correlate response (complete vs. partial vs. no change) measured by best appropriate imaging method after 6 weeks of treatment with pCR.

Primary Objective of the Supportive Anaemia Treatment Question:

For patients randomized to the supportive anemia treatment the primary objective of the supportive anemia treatment question was to compare the frequency of patients reaching hemoglobin (Hb) levels ≥11g/dl 6

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

weeks after treatment start of a first episode of anemia grade ≥2 (Hb <10g/dl) between patients receiving supportive treatment for iron deficiency with parenteral (IV) ferric carboxymaltose (FCM) versus physician's choice (PhCh) [no supportive treatment, oral iron substitution, erythropoiesis-stimulating agent (ESA), or both].

Secondary Objectives of the Supportive Anaemia Treatment Question:

For patients randomized to the supportive anemia treatment the secondary objectives for the supportive anemia treatment question were to:

- Compare the median time to achieve a hemoglobin level ≥11g/dl between the supportive treatment arms.
- Compare the frequency of patients with a hemoglobin level ≥11g/dl in the week after the end of the last chemotherapy cycle between the supportive treatment arms.
- Compare the median time to achieve an increase in Hb levels by 1g/dl between the supportive treatment arms.
- Compare the change in Hb versus baseline (=randomization in the anemia study) and weeks 4, 8, 12, 16, and EOT (i.e. day of surgery).
- Compare the transfusion rate (total number and per patient) and hospital admissions during the first episode of anemia between the supportive treatment arms.
- Compare toxicity and compliance in the two arms.
- Describe use of subsequent supportive anemia treatments in both arms.
- Compare the rate of subsequent episodes after successful treatment of the first anemic episode.
- Compare the change in iron parameters from baseline (= randomization in the anemia study) and weeks 4, 8, 12, 16, and EOT (i.e. day of surgery).
- Compare quality of life using the FACT-An anemia and fatigue questionnaire between the supportive treatment arms.

Methodology:

This was a multicenter, prospective, randomized, open-label Phase III study with two different dose-dense, dose-intensified approaches as neoadjuvant therapy in patients with untreated high-risk early breast cancer.

Patients were randomized in a 1:1 ratio to either ETC treatment or PM(Cb) treatment. Stratification factors for the chemotherapy randomization were:

- Breast cancer subtype (HER2+/HR+/- vs. HER2-/HR+ vs. HER2-/HR-) based on central testing
- Ki-67 at baseline (≤20% vs. >20%)
- LPBC at baseline (no vs. yes).

Patients with HER2-positive disease additionally received trastuzumab and pertuzumab simultaneously to all T and C cycles in the ETC arm and to all PM (Cb) cycles in the PM(Cb) arm.

Patients who developed an iron-deficient anemia grade ≥2 were randomized to either

- Physician's choice (no treatment, oral iron substitution, erythropoetin stimulating agents or both)

or

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

- Ferric carboxymaltose (Ferinject®) iv.

Randomization for the supportive anemia question was stratified by chemotherapy arm and planned physician's choice.

Study treatment was not blinded, however the pathologist in general was not informed about the specific chemotherapy and the histology reports were also centrally reviewed in a blinded fashion.

The conduct of the study was reviewed and monitored by a Protocol Board and an Independent Data Monitoring Committee.

The study also comprised 3 sub-studies: a sub-study investigating the potential of PET as an add-on diagnostic tool to reduce the frequency of mastectomy in patients with breast cancer treated with neoadjuvant chemotherapy, a pharmacogenetic sub-study, and a sub-study on ovarian function.

Results on sub-studies will be reported separately.

Number of patients (planned and analyzed):

The study planned to recruit 950 patients in approximately 80 – 100 study sites. In total, 961 patients in 57 study sites were randomized, 945 patients started treatment and were treated with either ETC (470 patients) or PM(Cb) (475 patients).

Diagnosis and Main Criteria for Inclusion:

The study included patients at least 18 years of age with unilateral or bilateral primary carcinoma of the breast, histologically confirmed by core biopsy and measurable disease (ie, tumor lesion in the breast with maximum diameter ≥ 2 cm by palpation or ≥ 1 cm by sonography; measurable in two dimensions).

Patients had to have stage cT1c - cT4a-d disease. Patients with HER2-positive or TNBC were eligible irrespective of nodal status (cN0-cN3). Patients with luminal B-like tumors (defined here as ER and/or PgR >1% stained cells, HER2 negative, Ki-67 >20%) only with histologically (sentinel-node biopsy, core- or fine-needle biopsy) involved lymph nodes (pN1-3).

ER, PR, HER2, Ki-67, and LPBC status had to be centrally confirmed from the core biopsy prior to randomization.

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

Investigational products in this study were epirubicin, cyclophosphamide, paclitaxel, NPLD, pertuzumab, trastuzumab, carboplatin, and ferric carboxymaltose.

Patients were treated with either:

- ETC treatment
  - Epirubicin 150mg/m², every 2 weeks for 3 cycles followed by
  - Paclitaxel 225 mg/m², every 2 weeks for 3 cycles followed by
  - Cyclophosphamide 2000 mg/m², every 2 weeks for 3 cycles

or

- PM(Cb) treatment
  - Paclitaxel 80mg/m², 18 times weekly simultaneously with

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

- NPLD (Myocet®) 20mg/m², 18 times weekly simultaneously with
- Carboplatin AUC 1.5, 18 times weekly (only in patients with TNBC).

Patients with HER2-positive disease received trastuzumab 6 mg/kg (8 mg/kg loading dose) every 3 weeks and pertuzumab 420 mg (840 mg loading dose) every 3 weeks simultaneously to all T and C cycles in the ETC arm (4 infusions) and to all PM (Cb) cycles in the PM(Cb) arm (6 infusions).

Ferric carboxymaltose (Ferinject®) was administered (i.v.) only in patients who were randomized for supportive anemia treatment. The schedule of administration was 1000 mg at Week 1 and 500 mg (if body weight was <70 kg) or 1000 mg (if body weight was ≥70 kg) at Week 2. In case, body weight was <50 kg, a maximum dose of 20 mg ferric carboxymaltose/kg body weight per week should not be exceeded.

Duration of Treatment:

PM(b) treatment: Paclitaxel, NPLD, and carboplatin were given Q1W. ETC treatment: Epirubicin, paclitaxel, and cyclophosphamide were given Q2W. The entire treatment period was 18 weeks.

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

See above for details on therapy and dose.

Doxorubicinhydrochloride Batch Numbers: 14F22DE, 14J11DE, 14K61DE, 15C41DE, 15F51DE, 15J11DE, 15K35DE, 16C51DE

Ferric Carboxymaltose Batch Numbers: 320111B, 3701013, 4350010B, 436201, 4742013, 4792013, 5321013A, 5362013B

Pertuzumab Batch Numbers: H0080B07, H0103B05, H0128B02

Criteria for Evaluation:

Efficacy:

Primary endpoint:

The primary efficacy endpoint of this study was pathological complete response (pCR=ypT0/is ypN0), defined as no microscopic evidence of residual invasive viable tumor cells in all resected specimens of the breast and axilla.

Secondary endpoints

- ypT0 ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT(any) ypN0 were defined according to the TNM classification (Edition 7).
- Clinical (c) and imaging (i) response was to be assessed every 6 weeks and before surgery by physical examination and imaging tests. Clinical (imaging) response of the breast was specified as complete response (CR), partial response (PR), stable disease (NC), and progressive disease (PD). Clinical response was reported before surgery (end of treatment) and early response at approximately 6 weeks of treatment.
- Response of the axillary nodes was defined as a) conversion from cN+ (by palpation) at baseline to cN0 by palpation before surgery and b) conversion from cN+ by palpation or sonography at baseline to ypN0 at surgery.
- Breast conservation was defined as tumor resection, segmental resection or quadrant resection as last surgical procedure.

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

- Additionally (not specified in the study protocol), axilla conservation, defined as SNB only (before or after chemotherapy).

Safety:

Safety objectives of the study were to assess the overall toxicity of the study including incidence of febrile neutropenia and cardiac dysfunction/failure and treatment compliance including frequency of dose delays and reductions per arm and subtype.

The corresponding endpoints were:

- Toxicity (adverse events, including pre-defined adverse events of special interest) was assessed according to the NCI-CTCAE version 4.0 except congestive heart failure which was assessed according to the NYHA class.
- Treatment compliance [dose reductions, treatment delays, treatment interruptions, skipped infusions, premature treatment discontinuations, relative total dose (RTD) and relative total dose intensity (RTDI)].

Statistical Methods:

Analyses were based on the modified intent-to-treat set (mITT) and the per protocol set.

Primary efficacy endpoint analysis:

The primary endpoint was summarized as pCR rate for each treatment group. Two-sided 95% confidence intervals were calculated according to Pearson and Clopper (Pearson, 1934). The difference in the rates of pCR between groups was evaluated as an odds ratio and its 95% confidence interval as well as an absolute difference and its 95% confidence interval. Significance was tested with the two-sided continuity corrected $\chi 2$-test with significance level of $\alpha = 0.05$. It was pre-planned in the study protocol that, if the superiority test failed to detect a significant difference, the non-inferiority was to be tested. The non-inferiority margin for the pCR rate difference was set to 5%, non-inferiority was to be claimed, if the lower limit of the 2-sided 95% interval for the pCR rate difference (PM(Cb) arm minus ETC arm) was greater than -5%. A secondary logistic regression analysis adjusting for the stratification factors was conducted. Uni- and multivariate logistic regressions were performed for pCR to report odds ratio with 95% CI and to adjust for different factors. The primary endpoint was also analyzed subgroups. There was no adjustment for multiple comparisons in the analyses in subgroups. The subgroup analysis is to be considered explorative. A Breslow-Day interaction test was performed to assess interaction between treatment arm and binary subgroup; for the breast cancer subtype a logistic regression with an interaction term was performed to assess interaction. A STEPP analysis (tail-oriented, with 9 groups) was performed in each arm to explore influence of the RTDI on the pCR rate (Bonetti, 2004).

Secondary efficacy endpoint analysis:

Short-term secondary efficacy endpoints (clinical and imaging response rates, ypT0 ypN0, ypT0, ypT0/is, ypN0, breast and axilla conservation) were analyzed in the mITT set.

The secondary endpoints clinical and imaging response rates of breast after 6 weeks of treatment and before surgery, ypT0 ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT(any) ypN0, breast conservation, and axilla conservation were summarized as number and percent of patients for each treatment group. Two-sided 95% confidence intervals were calculated according to Pearson and Clopper and odds ratios between treatment groups from univariate logistic regression were reported for all of them, as well as the difference in the rates and its 95% CI. The rates of axilla conversion were reported per treatment arm in patients with nodal-positive disease at baseline. A 2-sided continuity corrected $\chi 2$ test was used to compare clinical and imaging response rates of breast and lymph nodes, ypT0 ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT(any), ypN0, breast

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

conservation, and axillary conservation between treatment arms. Univariate and multivariate logistic regressions were performed for ypT0 ypN0 to report odds ratios with 95% CI and to adjust for factors. The key secondary short-term endpoint pCR ypT0 ypN0 was also analyzed in subgroups. There was no adjustment for multiple comparisons in the analyses in subgroups which are considered explorative. In the subgroup analysis of ypT0 ypN0, a Breslow-Day interaction test was performed to assess interaction between treatment arm and binary subgroup; for the breast cancer subtype a logistic regression with an interaction term was performed to assess interaction.

SUMMARY

Efficacy Results:

In the GeparOcto study a total of 945 patients started therapy, of those 938 (99.3%) underwent surgery. Overall, 227 out of 470 patients who started ETC [48.3% (95% CI: 43.7%, 52.9%)] achieved a pCR (ypT0/is ypN0) compared to 228 out of 475 who started PM(Cb) [48.0% (95% CI: 43.4%, 52.6%)]; continuity corrected $\chi 2$-test p=0.979, corresponding to an OR of 0.99 (95% CI: 0.77-1.28).

Table: Primary efficacy endpoint: pCR (ypT0/is ypN0) (mITT population)

Parameter	ETC (N=470) n (%)	PM(Cb) (N=475) n (%)	Overall (N=945) n (%)	p-value
No	243 (51.7)	247 (52.0)	490 (51.9)	0.979
Yes	227 (48.3)	228 (48.0)	455 (48.1)	
95% CI	(43.7%, 52.9%)	(43.4%, 52.6%)		
Difference, 95% CI			-0.3% (-6.7%, 6.1%)	

CI = Confidence interval; ETC = Epirubicin, Paclitaxel, Cyclophosphamide; mITT = Modified intent-to-treat; pCR = Pathological complete response; PM(Cb) = Paclitaxel, NPLD, Carboplatin

There were no differences between treatment groups in pCR rates according to other definitions or for other secondary efficacy endpoints.

Table: pCR rates analyzed as secondary endpoints [ypT0 ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT0(any) ypN0] (mITT population)

Secondary endpoint definitions of pCR	ETC (N=470) n (%)	PM(Cb) (N=475) n (%)	Overall (N=945) n (%)	p-value
ypT0, ypN0				
No	275 (58.5)	269 (56.6)	544 (57.6)	0.604
Yes	195 (41.5)	206 (43.4)	401 (42.4)	
95% CI	(37.0%, 46.1%)	(38.9%, 48.0%)		
Difference, 95% CI			1.9% (-4.4%, 8.2%)	
ypT0, ypN0/+				
No	254 (54.0)	244 (51.4)	498 (52.7)	0.448
Yes	216 (46.0)	231 (48.6)	447 (47.3)	

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

95% CI	(41.4%, 50.6%)	(44.1%, 53.2%)		
Difference, 95% CI			2.7% (-3.7%, 9.0%)	
ypT0/is, ypN0/+				
No	216 (46.0)	217 (45.7)	433 (45.8)	0.985
Yes	254 (54.0)	258 (54.3)	512 (54.2)	
95% CI	(49.4%, 58.6%)	(49.7%, 58.9%)		
Difference, 95% CI			0.3% (-6.1%, 6.6%)	
ypT(any), ypN0				
No	116 (24.7)	129 (27.2)	245 (25.9)	0.427
Yes	354 (75.3)	346 (72.8)	700 (74.1)	
95% CI	(71.2%, 79.2%)	(68.6%, 76.8%)		
Difference, 95% CI			-2.5% (-8.1%, 3.1%)	

CI = Confidence interval; ETC = Epirubicin, Paclitaxel, Cyclophosphamide; mITT = Modified intent-to-treat; pCR = Pathological complete response; PM(Cb) = Paclitaxel, NPLD, Carboplatin

In most of the stratified and prospectively defined subgroups the pCR (ypT0/is ypN0) rate was not significantly different in the two treatment arms. According to biological subtype, the pCR rates for ETC vs. PM(Cb) was 14.1% vs. 14.6% in the HER2-negative/HR-positive cohort (N=160; p=1.000), 48.5% vs. 51.7% in the TNBC cohort (N=403; p=0.584), and 62.0% vs. 58.4% in the HER2-positive cohort (N=382; p=0.545). In patients with high Ki-67 (>20%) tumors (N=885), pCR was 49.0% vs. 48.0% (p=0.816) and in patients with low Ki-67 tumors (N=60) 37.9% vs. 48.4% (p=0.578). In patients without LPBC (N=822), pCR was 44.1% vs. 46.4% (p=0.571) and in patients with LPBC (N=123) 76.7% vs. 58.7% (p=0.054). Logistic regression analysis, however, showed that the proportion of patients achieving a pCR was significantly higher in the LPBC subgroup when patients were treated with ETC as compared to PM(Cb) [OR PM(Cb) vs. ETC: 0.43; 95% CI: 0.20-0.95, p=0.036]. The test for interaction for the treatment effect in patients with LPBC vs. patients without LPBC on the pCR rate was significant (p=0.027). In all other stratified subgroups, no effect of treatment on the pCR rate could be seen. Multivariable logistic regression analysis confirmed, that treatment with PM(Cb) did not predict for achievement of pCR after adjustment for baseline and stratification factors (OR: 0.99; 95% CI: 0.75-1.31; p=0.931). Among the stratification factors, biological subtype (TNBC OR: 5.39, 3.20–9.07, p<0.001; HER2+ OR: 9.78, 5.80–16.5, p<0.001 compared to HER2-/HR+) and LPBC (OR: 2.28, 1.48–3.52, p<0.001 compared to no LPBC) were independent predictors for achievement of pCR.

Clinical (imaging) response of the breast tumor after six weeks of treatment was statistically significantly in favor of PM(Cb) treatment with respect to ORR [PM(Cb) treatment: 79.4%; ETC treatment: 71.5%] with p=0.006. This difference was not maintained at the investigation before surgery [PM(Cb) treatment: 88.2%; ETC treatment: 89.6%] (p=0.573).

Response rate of the axillary nodes did not statistically significantly differ between the treatment groups. This was the case for both, axillary nodes that converted to cN0 as determined by palpation [ETC treatment: 67.3%; PM(Cb) treatment: 67.6%; p=1.00] and conversion to ypN0 as determined by histology [ETC treatment: 63.7%; PM(Cb) treatment: 63.0%; p=0.975].

Both treatment arms did not differ with respect to the percentage of the different type of surgery (p=1.000); breast conservation rates were almost identical in both treatment arms [ETC treatment: 68.7%, PM(Cb) treatment: 68.6%].

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

Both treatment arms did not relevantly differ with respect to the percentage of patients with axilla conservation (p=0.325); axilla conservation rates were comparable in both treatment arms [ETC treatment: 47.1%, PM(Cb) treatment: 50.5%].

Safety Results:

Across all biological subgroups, treatment discontinuations were less common in patients treated with ETC compared to PM(Cb) (HER2-/HR+: 14.1% vs. 30.5%, p=0.013; HER2-/HR-: 16.5% vs. 34.5%, p<0.001; HER2+: 17.2% vs. 35.3%, p<0.001). The chemotherapy dose was delayed in 351 patients (74.7%) in the ETC arm compared with 420 (88.4%) in the PM(Cb) arm (p<0.001). These delays were due to hematological toxicity in 23.2% vs 31.6% (p=0.004) and due to other non-hematological toxicities in 25.7% vs 52.8% (p<0.001), respectively. The chemotherapy dose had to be reduced in 216 (46.0%) in the ETC arm compared with 271 (57.1%) in the PM(Cb) arm (p<0.001), which was due to hematological toxicity in 24.3% vs 13.3% (p<0.001) and due to other non-hematological toxicities in 27.2% vs 42.3% (p<0.001), respectively. A total of 14 (3.0%) patients in the ETC arm and 74 (15.6%) in the PM(Cb) arm skipped an infusion (p<0.001), none vs 1.7% (p=0.008) due to hematological toxicity and 3.0% vs 13.1% (p<0.001) due to other non-hematological toxicities, respectively.

Hematological adverse events were more frequent with ETC treatment. In 469 (99.8%) patients with ETC treatment and in 464 (97.7%) with PM(Cb) treatment any hematological event of any grade (p=0.006) were reported and in 423 (90.0%) and 137 (28.8%) patients any hematological event of grade 3-4 (p<0.001) were reported, respectively. Rates of toxic treatment effects such as anemia, leukopenia, neutropenia, febrile neutropenia, thrombopenia and increased values for alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase and creatinine were all higher in the ETC arm.

There was no significant difference between the treatment arms for reports on any non-hematological adverse events any grade with 470 (100%) patients in the ETC arm and 474 (99.8%) in the PM(Cb) arm (p=1.00), but any non-hematological grade ≥3 adverse events were higher in the PM(Cb) arm: 203 (43.2%) vs. 47 (52.0%), respectively (p=0.008). Among the high grade adverse events, pneumonia was reported in 4 (0.9%) patients in the ETC and 31 (6.5%) in the PM(Cb) arm (p<0.001) and pneumonitis, which was a predefined adverse event of special interest (AESI), in 0 (0%) and 12 (2.5%), respectively (p<0.001).

Table: Hematological and pre-defined non-hematological AEs of any grade (1-4), if reported in at least 1% of the safety population [1]

Hematological/pre-defined non-hematological AE (any grade)	**ETC (N=470) n (%)**	**PM(Cb) (N=475) n (%)**	**Overall (N=945) n (%)**	**p-value [2]**
Anemia	466 (99.1)	437 (92.0)	903 (95.6)	<0.001
Leukopenia	450 (95.7)	401 (84.4)	851 (90.1)	<0.001
Alopecia	412 (87.7)	421 (88.6)	833 (88.1)	0.688
Peripheral sensory neuropathy	392 (83.4)	345 (72.6)	737 (78.0)	<0.001
Neutropenia	422 (89.8)	305 (64.2)	727 (76.9)	<0.001
Fatigue and asthenia	372 (79.1)	342 (72.0)	714 (75.6)	0.012
Skin reactions	252 (53.6)	364 (76.6)	616 (65.2)	<0.001
Mucositis	270 (57.4)	312 (65.7)	582 (61.6)	0.011
Increased ALAT	346 (73.6)	234 (49.4)	580 (61.4)	<0.001
Nausea	316 (67.2)	236 (49.7)	552 (58.4)	<0.001

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

Thrombopenia	367 (78.1)	145 (30.5)	512 (54.2)	<0.001
Increased AP	300 (64.9)	182 (39.3)	482 (52.1)	<0.001
Infection other than pneumonia	205 (43.6)	252 (53.1)	457 (48.4)	0.004
Diarrhea	191 (40.6)	262 (55.2)	453 (47.9)	<0.001
Increased ASAT	208 (44.3)	134 (28.3)	342 (36.2)	<0.001
Stomatitis	156 (33.2)	174 (36.6)	330 (34.9)	0.276
Arthralgia	207 (44.0)	103 (21.7)	310 (32.8)	<0.001
Myalgia	175 (37.2)	97 (20.4)	272 (28.8)	<0.001
Headache	152 (32.3)	117 (24.6)	269 (28.5)	0.009
Fever without neutropenia	107 (22.8)	146 (30.7)	253 (26.8)	0.007
Anorexia	117 (24.9)	88 (18.5)	205 (21.7)	0.018
Epistaxis	59 (12.6)	132 (27.8)	191 (20.2)	<0.001
Dyspnea	93 (19.8)	87 (18.3)	180 (19.0)	0.619
Vomiting	103 (21.9)	67 (14.1)	170 (18.0)	0.002
Allergic reactions	88 (18.7)	57 (12.0)	145 (15.3)	0.005
Increased serum creatinine	57 (12.1)	28 (5.9)	85 (9.0)	<0.001
Thromboembolic event	28 (6.0)	55 (11.6)	83 (8.8)	0.003
Febrile neutropenia	60 (12.8)	16 (3.4)	76 (8.0)	<0.001
Increased bilirubin	32 (6.8)	20 (4.2)	52 (5.5)	0.088
Pneumonia	5 (1.1)	46 (9.7)	51 (5.4)	<0.001
Pneumonitis [3]	3 (0.6)	21 (4.4)	24 (2.5)	<0.001
LVEF>=10% decrease from baseline and <50% [4]	5 (1.1)	5 (1.1)	10 (1.1)	1.000
Other AE, reported as free-text	427 (90.9)	434 (91.4)	861 (91.1)	0.820

AE = Adverse event; ALAT = Alanine aminotransferase; AP = Alkaline phosphatase; ASAT = Aspartate aminotransferase; ETC = Epirubicin, Paclitaxel, Cyclophosphamide; LVEF = Left ventricular ejection fraction; PM(Cb) = Paclitaxel, NPLD, Carboplatin

[1] Missing values not listed.
[2] p-value for comparison of ETC and PM(Cb) treatment
[3] AE of special interest, if grade 2 or higher
[4] AE of special interest

Table: Other AEs of any grade (1-4), if reported in at least 1% of the safety population [1]

Other AEs (any grade)	ETC (N=470) n (%)	PM(Cb) (N=475) n (%)	Overall (N=945) n (%)	p-value [2]
Nail disorders	119 (25.3)	192 (40.4)	311 (32.9)	<0.001
Constipation	135 (28.7)	128 (26.9)	263 (27.8)	0.562

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

Taste and smell disorders	125 (26.6)	112 (23.6)	237 (25.1)	0.294
Other gastrointestinal disorders	112 (23.8)	124 (26.1)	236 (25.0)	0.452
Bone pain	123 (26.2)	47 (9.9)	170 (18.0)	<0.001
Dizziness	87 (18.5)	69 (14.5)	156 (16.5)	0.115
Hot flushes	79 (16.8)	66 (13.9)	145 (15.3)	0.241
Eye disorders	67 (14.3)	69 (14.5)	136 (14.4)	0.926
Sleep disorders	62 (13.2)	60 (12.6)	122 (12.9)	0.846
Pyrosis	45 (9.6)	74 (15.6)	119 (12.6)	0.006
Edema	56 (11.9)	59 (12.4)	115 (12.2)	0.843
Other respiratory disorders	44 (9.4)	70 (14.7)	114 (12.1)	0.012
Other vascular disorders	61 (13.0)	51 (10.7)	112 (11.9)	0.315
Cough	52 (11.1)	50 (10.5)	102 (10.8)	0.834
Other musculo-skeletal disorders	48 (10.2)	48 (10.1)	96 (10.2)	1.000
Other nervous system disorders	41 (8.7)	48 (10.1)	89 (9.4)	0.505
Other general disorders	52 (11.1)	35 (7.4)	87 (9.2)	0.056
Upper abdominal pain	41 (8.7)	41 (8.6)	82 (8.7)	1.000
Back pain	39 (8.3)	42 (8.8)	81 (8.6)	0.817
Other skin and subcutaneous tissue disorders	25 (5.3)	41 (8.6)	66 (7.0)	0.055
Pain	40 (8.5)	24 (5.1)	64 (6.8)	0.038
Other psychiatric disorders	35 (7.4)	27 (5.7)	62 (6.6)	0.295
Chills	15 (3.2)	43 (9.1)	58 (6.1)	<0.001
Tachycardia	29 (6.2)	26 (5.5)	55 (5.8)	0.679
Other renal and urinary disorders	26 (5.5)	26 (5.5)	52 (5.5)	1.000
Dry skin	24 (5.1)	26 (5.5)	50 (5.3)	0.885
Injury and poisoning, procedural complications	11 (2.3)	35 (7.4)	46 (4.9)	<0.001
Other cardiac disorders	25 (5.3)	16 (3.4)	41 (4.3)	0.153
Reproductive disorders	20 (4.3)	21 (4.4)	41 (4.3)	1.000
Other metabolism and nutrition disorders	16 (3.4)	21 (4.4)	37 (3.9)	0.503
Ear and labyrinth disorders	15 (3.2)	20 (4.2)	35 (3.7)	0.492
Other hepato-biliary disorders	16 (3.4)	19 (4.0)	35 (3.7)	0.731
Other blood and lymphatic system disorders	20 (4.3)	5 (1.1)	25 (2.6)	0.002
Investigations	10 (2.1)	10 (2.1)	20 (2.1)	1.000

AE = Adverse event; ETC = Epirubicin, Paclitaxel, Cyclophosphamide; PM(Cb) = Paclitaxel, NPLD, Carboplatin

[1] Missing values not listed.

[2] p-value for comparison of ETC and PM(Cb) treatment

Overall, 345 (36.5%) patients reported at least one serious adverse event, 174 (37.0%) in the ETC arm and 171 (36.0%) in the PM(Cb) arm (p=0.787) and 41 (4.3%) at least one AESI, 12 (2.6%) in the ETC and 29

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

(6.1%) in the PM(Cb) arm (p=0.010), which were treatment related in 11 (2.3%) and 28 (5.9%) patients, respectively (p=0.008).

Most prominent differences between the treatment groups with higher frequencies in the ETC treatment arm were observed for the System Organ Class blood and the lymphatic system disorders ([ETC: 126 SAEs, PM(Cb): 20 SAEs] and with higher frequencies in the PM(Cb) treatment arm for the System Organ Classes infections and infestations ([ETC: 23 SAEs, PM(Cb): 69 SAEs], respiratory, thoracic and mediastinal disorders ([ETC: 8 SAEs, PM(Cb): 19 SAEs], and vascular disorders ([ETC: 6 SAEs, PM(Cb): 16 SAEs].

With respect to Preferred Terms most prominent differences between the treatment groups with higher frequencies in the ETC treatment arm were observed for febrile neutropenia ([ETC: 43 SAEs, PM(Cb): 10 SAEs], neutropenia ([ETC: 40 SAEs, PM(Cb): 0 SAEs], leukopenia ([ETC: 26 SAEs, PM(Cb): 3 SAEs], and general physical health deterioration ([ETC: 13 SAEs, PM(Cb): 3 SAEs]. Most pronounced higher frequencies in the PM(Cb) treatment arm were reported for pneumonia ([ETC: 3 SAEs, PM(Cb): 31 SAEs], diarrhea ([ETC: 3 SAEs, PM(Cb): 21 SAEs], and pneumonitis ([ETC: 2 SAEs, PM(Cb): 15 SAEs].

Table: Serious adverse events by System Organ Class and Preferred Term (Preferred terms are listed if they occurred more than twice) (safety population)

System Organ Class Preferred Term	ETC (N=470) No. of SAEs	PM(Cb) (N=475) No. of SAEs	Overall (N=945) No. of SAEs
Total number of SAEs	**287**	**247**	**534**
Blood and the lymphatic system disorders	**126**	**20**	**146**
Febrile neutropenia	43	10	53
Neutropenia	40	0	40
Leukopenia	26	3	29
Pancytopenia	9	1	10
Anaemia	1	6	7
General disorders and administration site conditions	**61**	**52**	**113**
Pyrexia	40	43	83
General physical health deterioration	13	3	16
Fatigue	1	4	5
Asthenia	3	1	4
Infections and infestations	**23**	**69**	**92**
Pneumonia	3	31	34
Urinary tract infection	3	6	9
Infection	3	3	6
Device related infection	1	4	5

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

Abscess	1	2	3
Atypical pneumonia	0	3	3
Bronchitis	1	2	3
Influenza	2	1	3
Tonsillitis	0	3	3
Gastrointestinal disorders	**29**	**33**	**62**
Diarrhoea	3	21	24
Vomiting	5	2	7
Mucosal inflammation	4	2	6
Nausea	6	0	6
Stomatitis	4	1	5
Respiratory, thoracic and mediastinal disorders	**8**	**19**	**27**
Pneumonitis	2	15	17
Dyspnoea	4	2	6
Vascular disorders	**6**	**16**	**22**
Embolism	2	5	7
Thrombosis	2	4	6
Deep vein thrombosis	0	3	3
Pulmonary embolism	0	3	3
Nervous system disorders	**9**	**7**	**16**
Musculoskeletal, connective tissue and bone disorders	**8**	**2**	**10**
Back pain	2	1	3
Cardiac disorders	**4**	**5**	**9**
Ejection fraction decreased	2	1	3
Injury, poisoning and procedural complications	**2**	**5**	**7**
Spinal fracture	0	3	3
Skin and subcutaneous tissue disorders	**1**	**5**	**6**
Palmar-plantar erythrodysaesthesia syndrome	0	5	5
Metabolism and nutrition	**1**	**4**	**5**
Hypokalaemia	1	2	3
Hepato-biliary disorders	**1**	**4**	**5**
Immune system disorders	**3**	**1**	**4**
Psychiatric disorders	**1**	**3**	**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: Various	Volume:	
Name of active ingredient: Various	Page:	

Reproductive system and breast disorders	**2**	**0**	**2**
Investigations	**1**	**1**	**2**
Ear and labyrinth disorders	**0**	**1**	**1**
Renal and urinary disorders	**1**	**0**	**1**

ETC = Epirubicin, Paclitaxel, Cyclophosphamide; PM(Cb) = Paclitaxel, NPLD, Carboplatin; SAE = Serious adverse event

Two deaths under therapy occurred in the PM(Cb) arm, one due to pneumonia and one due to multiple septic cerebral embolism. Both deaths were considered related to the study treatment by the investigators.

Results of the Supportive Anaemia Treatment Question

Less than anticipated patients had chemotherapy-induced anaemia. A total of 125 patients were randomised, 62 in FCM and 63 in PhCh arm.

Primary endpoint: after 6 weeks, overall 40 (32.0%) of patients (22 in FCM and 18 in PhCh arm; p=0.447) reached Hb level of ≥11g/dl.

Secondary endpoints:

- Median time to achieve Hb ≥ 11 g/dl was 9.0 weeks (95%CI 5.0–not reached) with FCM vs. 10.6 weeks by PhCh (95%CI 5.9–14.3) corresponding to hazard ratio (HR) 1.17 (95%CI 0.67–2.03).
- Rate of patients who achieved Hb ≥ 11 g/dl in the week after the end of the last chemotherapy cycle was 41.9% (26/62) with FCM vs. 39.7% (25/63) by PhCh (p=0.857).
- Median time to achieve improvement in Hb level by 1 g/dl was 5.0 weeks (95%CI 2.4–8.0) with FCM vs. 5.0 weeks (95% CI 3.0–12.1) by PhCh corresponding to HR 1.09 (95%CI 0.67–1.78).
- Median Hb changes at different time points vs. baseline were comparable in both arms during the anaemia treatment (FCM: from 0.8 g/dl at 4 weeks to 1.7 g/dl at 16 weeks and PhCh: 0.7 g/dl-2.2 g/dl) as well as at EOT (FCM and PhCh 0.8 g/dl).
- Blood transfusion until 6 weeks of therapy received 2 patients in FCM and 5 in PhCh arm (p=0.246), whereas after 6 weeks of therapy it was performed in 5 patients in FCM and one in PhCh arm (p=0.205).
- Among patients assigned to the FCM arm, 2 patients did not receive any FCM dose, 6 received only one FCM dose, and in 6 patients the first FCM dose and in 30 patients the second FCM dose was reduced. In the PhCh arm, of the 15 patients stratified to no supportive anaemia treatment, 11 did actually not receive any treatment; of the 20 patients stratified to receive oral iron substation, 15 did; of the 8 patients stratified to receive ESAs, 4 did; of the 9 patients stratified to receive both anaemia treatments, 2 did.
- After 6 weeks of anemia treatment, 80.5% of patients in FCM vs. 68.1% in PhCh arm did not require a subsequent anaemia therapy, whereas 2.4% in FCM and 14.9% in the PhCh arm received oral iron substitution; 17.1% in the FCM and 14.9% in the PhCh arm were treated with ESAs and only 2.1% of patients in the PhCh arm received both therapies.
- During the anaemia treatment, median serum ferritin changes and median transferrin saturation (TSAT) changes at different time points vs. baseline were in general higher in FCM as compared with PhCh arm, e.g at 4 weeks the median serum ferritin was 1105.5 ng/ml vs. 15.0 ng/ml, and the

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

median TSAT was 13% vs. 3%. At EOT the median serum ferritin change was significantly higher in FCM vs. PhCh arm (340.0 vs. 0.0 ng/ml; p<0.001), while the median TSAT change was not significantly different between the two arms (9.0% vs.5.0%; p=0.065).

- The quality of life measured by FACT-An questionnaires was comparable between the two arms.

CONCLUSIONS:

Main study

In high-risk early stage breast cancer patients, weekly PM(Cb) did not result in higher pCR (ypT0/is ypN0) rates compared to ETC. Non-inferiority of PM(Cb) could not be shown but PM(Cb) was associated with a higher rate of pneumonia and pneumonitis and other grade 3-4 non-hematological adverse events than ETC. Interestingly, patients with an LPBC tumor achieve a significantly higher pCR rate with ETC. Overall, PM(Cb) appeared to be less feasible than ETC for the treatment of high-risk early stage breast cancer patients.

Supportive Anaemia Treatment Question

This is the first study investigating IV iron treatment for dose-dense chemotherapy-induced anaemia in breast cancer. Overall, 32% of patients reached Hb ≥ 11 g/dl at 6 weeks, irrespective of anaemia therapy. FCM treatment was not different than PhCh for anaemia therapy.

Date of the Report:

19-Jul-2019

Annex 1

Amendment to Protocol

There was one substantial Amendment to the protocol of GeparOcto pertaining to the supportive anemia treatment:

The originally estimated number of iron deficiency anaemias had been found to be too high due to the set value for one parameter. However, to be able to evaluate the additional issue of iron deficiency anemia, the threshold for serum ferritin was raised (from <300 ng / dl) to <600 ng / dl via Amendment 1 in order to be able to randomize more patients.

In addition, several updates to the reference document for the investigational medicinal product pertuzumab required appropriate adjustments in patient informed consent.

Note on the Batch Numbers:
Batch numbers are only available for the provided IMPs Doxorubicin Hydrochloride, Ferric Carboxymaltose and Pertuzumab.