CLINICAL STUDY REPORT

A PROSPECTIVE, RANDOMISED MULTI-CENTRE PHASE II STUDY EVALUATING THE ADJUVANT, NEOADJUVANT OR PALLIATIVE TREATMENT WITH TAMOXIFEN +/- GnRH ANALOGUE VERSUS AROMATASE INHIBITOR + GnRH ANALOGUE IN MALE BREAST CANCER PATIENTS

(GBG 54 - MALE study)

EudraCT no.: 2009-015122-11

Investigational Products:	Exemestan (AROMASIN®) Goserelin Leuprorelin Tamoxifen
Indication:	Male Breast Cancer
Study Protocol:	Protocol (April 2nd, 2012) Amendment 1 (July 22nd, 2016)
Phase:	2
Report Version:	Number 2
First Patient Enrolled:	October 22nd, 2012
Last Patient Completed:	November 28th, 2017

Co-ordinating Investigator:
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Sponsor:
GBG Forschungs GmbH
Martin-Behaim-Straße 12, 63263 Neu-Isenburg

Date of this report: October 14th, 2020

SYNOPSIS

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Name of active ingredient: Exemestane Goserelin Leuprorelin Tamoxifen		

Title of Study:
A prospective, randomised multi-centre phase II study evaluating the adjuvant, neoadjuvant or palliative treatment with tamoxifen +/- GnRH analogue versus aromatase inhibitor + GnRH analogue in male breast cancer patients.

Co-ordinating Investigator:
Dr. Mattea Reinisch
Kliniken Essen-Mitte

Study Centers:
The study was conducted at 35 sites in Germany:

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- Klinikum St. Marien Amberg, Frauenklinik, Mariahilfbergweg 5-7, 92224 Amberg (PI: Dr. Tanja Hauzenberger)
- Evangelisches Krankenhaus Bergisch Gladbach, Gynäkologie, Ferrenbergstr. 24, 51465 Bergisch-Gladbach (PI: Dr. Benno Nuding)
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- Universitätsfrauenklinik Bonn, Sigmund-Freud-Str. 25, 53105 Bonn (PI: Dr. Andrea Hocke)
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- Donau-Isar Klinikum Deggendorf, Abteilung für Senologie, Perlasberger Straße 41, 94469 Deggendorf (PI: Dr. Doris Augustin)
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- Kliniken Essen-Mitte, Evang. Huyssens-Stiftung/Knappschaft GmbH, Klinik für Senologie/Brustzentrum, Henricistr. 92, 45136 Essen (PI: Dr. Mattea Reinisch)
- Universitätsklinikum Essen, Klinik für Frauenheilkunde und Geburtshilfe / Brustzentrum, Hufelandstrasse 55, 45122 Essen (PI: PD Dr. Oliver Hoffmann)
- Universitätsklinikum Freiburg, Frauenklinik, Hugstetterstr. 55, 79106 Freiburg (PI: Dr. Beate Rautenberg)
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- Universitätsklinikum Ulm, Frauenklinik, Prittwitzstrasse 43, 89075 Ulm (PI: Prof. Dr. Wolfgang Janni)
- Rems-Murr-Klinik Winnenden, Frauenklinik, Am Jakobsweg 1, 71364 Winnenden (PI: Dr. Hans-Joachim Strittmatter)
- Marienhospital Witten, Brustzentrum, Marienplatz 2, 58452 Witten (PI: Dr. John Hackmann)

Publication (references):

1. Linder M, von Minckwitz G, Kamischke A, Rudlowski C, Eggemann H, Nekljudova V and Loibl S. A prospective, randomised multi-centre phase II study evaluating the adjuvant, neoadjuvant or palliative treatment with tamoxifen +/− GnRH analogue versus aromatase inhibitor + GnRH analogue in male breast cancer patients (GBG-54 MALE). Cancer Res 2012; (72) (24 Supplement). Abstract OT2-2-05.
2. Reinisch M, Seiler S, Hauzenberger T, Schmatloch S, Strittmatter HJ, Zahm DM et al. Male-GBG54: A prospective, randomised multi-centre phase II study evaluating endocrine treatment with either tamoxifen +/- gonadotropin releasing hormone analogue (GnRHa) or an aromatase inhibitor + GnRHa in male breast cancer patients. Cancer Res 2018; (78) (4 Supplement). Abstract PD7-10
3. Reinisch M, Seiler S, Hauzenberger T, Schmatloch S, Strittmatter HJ, Zahm DM et al. Final analysis of the Male-GBG54 study: A prospective, randomised multi-centre phase II study evaluating endocrine treatment with either tamoxifen +/- gonadotropin releasing hormone analogue (GnRHa) or an aromatase inhibitor + GnRHa in male breast cancer patients. Annals of Oncology 2018; 29:8 Abstract 273PD_PR.

Study Period (years):
Date of the first patient enrolled: October 22nd, 2012
Date of the last patient completed: November 28th, 2017

Phase of Development:
Phase II study

Objectives:

Primary Objective
To determine the efficacy of estradiol suppression between the three treatment arms after three months by a standardized procedure for routine testing.

Secondary Objectives
Efficacy:
- To determine the estradiol suppression between the three treatment arms after six months
- To compare testosterone, dihydrotestosterone (DHT), sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), osteocalcin and C-terminal telopeptide of type I collagen (CTX) in the three treatments arms. Note: it was decided in agreement with the central laboratory

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not to measure CTX since it is sensitive to the conditions under which the sample was obtained (time of the day, fasting) and would have a lot of variation in this study; additionally, free androgene index (FAI) was computed from testosterone and SHBG.

- To compare the efficacy in terms of overall response (for neoadjuvant and metastatic patients) in the three treatment arms. Note: since only 3 metastatic patients and no neoadjuvant patients were randomized, this objective could not be analysed.

Safety:

- To determine the safety and side effect parameters (at every visit):
  - Prostate-Specific Antigen (PSA) and haemoglobin, at three and six months
  - Lipids (total cholesterol, high density lipid (HDL) cholesterol, low density lipid (LDL) cholesterol), at three and six months
  - Adverse events according to National Cancer Institute Common Toxicity Criteria version 4.0, at three and six months.

Compliance:

- To compare the compliance in the three treatment arms.

Quality of Life:

- To compare the scores according to Male Questionnaires:
  - International Index of Erectile function (IIEF)
  - Aging Male Symptom Score (AMS)
  - International Prostate Symptom Score (IPSS).

Translational research objectives:

The translational research analysis of paraffin-embedded tumor tissue and blood samples for molecular-genetic analyses:

- Determination of cytochrome P450 polymorphisms
- Determination of hormone receptor activity (estrogen receptor, progesterone receptor, androgen receptor) and aromatase expression of the tumor tissue.

Translational research objectives are not part of this report.

Methodology:

The MALE study was a prospective, randomized, open-label multicenter phase II study. The patients have been randomly allocated in 1:1:1 ratio into one of three study arms:

- Arm A: Tamoxifen 20 mg (standard therapy).
- Arm B: Tamoxifen 20 mg + gonadotropin releasing hormone analogue (GnRH).
- Arm C: Aromatase inhibitor (Exemestane 25 mg) + GnRH analogue.

All treatments have been given for six months (further treatment according to the Arbeitsgemeinschaft

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Gynäkologische Onkologie guidelines).

The standardised determination of hormone levels at baseline, after three and six months of treatment have been measured in a central laboratory.

Number of patients (planned and analyzed):
Planned n= 48 evaluable patients, enrolled and randomized n=56, started treatment (mITT set) n=52; analyzed for safety, compliance and QoL n=52; analyzed for efficacy: primary objective (estradiol assessment after three months) and other hormones assessment after three months (secondary objectives) n=50, other secondary objectives (hormones assessment after six months) n=46.

Diagnosis and Main Criteria for Inclusion:
The study included female and male patients of at least 18 years of age with unilateral or bilateral carcinoma of the breast at primary diagnosis. Tumor has to be hormone receptor positive (e.g. estrogen receptor and/or progesterone receptor positive). Enrolment was possible in the neo-adjuvant, adjuvant and metastatic situation. Adequate surgical treatment with histological complete resection including axillary lymph nodes was required if patients were included as adjuvant treatment.

Test Products, Dose and Mode of Administration:
Exemestane (AROMASIN®)

- Dose: 25 mg
- Route: per os
- Schedule: each day one tablet, no interruption
- Duration: continuously for six months or until progression, patient's request or withdrawal from the study (whatever comes first).

Gonadotropin Releasing Hormone (GnRH) analogue; goserelin (ZOLADEX®) or leuprorelin (TRENANTONE®) used according to investigators choice.

- Dose and route: According to the manufacturer´s summary of product characteristics
- Schedule: once every three months (twice within the study)
- Duration: for six months or until progression, patient's request or withdrawal from the study (whatever comes first).

Tamoxifen

- Dose: 20 mg
- Route: per os
- Schedule: each day one tablet, no interruption
- Duration: continuously for six months or until progression, patient's request or withdrawal from the study (whatever comes first).

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Duration of Treatment: See above.		
Reference Therapy, Dose and Mode of Administration, Batch Number: Tamoxifen. See above for details on therapy and dose. *Batch numbers:* The batch number of the Investigational Medicinal Product exemestane (AROMASIN®) was: 118 AB. All other IMPs were not supplied by the sponsor but used as marketed drugs, so there is no information about the batch number available.		
Criteria for Evaluation: *Efficacy* The primary endpoint is • The difference of the 17-ß-estradiol level (in ng/L) from baseline to month 3. Secondary efficacy endpoints are: • The difference of the 17-ß-estradiol level (in ng/L) from baseline to month 6. • Changes in testosterone (µg/L), dihydrotestosterone (DHT, ng/L), SHBG (nmol/L), FAI, FSH (IU/L), LH (IU/L), osteocalcin (µg/L) in the three treatment arms from baseline to month 3 and month 6 • Overall response (for neoadjuvant and metastatic patients) in the three treatment arms. *Handling of laboratory data under the limit of detection and over the limit of quantitation* The minimal detectable values (limit of detection, LD) for the laboratory parameters are: Osteocalcin, 0.4 µg/L; FSH, 0.3 IU/L; LH, 0.1 IU/L; Estradiol, 5 ng/L; Testosterone, 0.1 µg/L; FAI, 1; SHBG, 0.8 nmol/L; DHT, 30 ng/L. For the measurements where the value was under limit of detection, "<LD" is reported in the laboratory data. For the analysis these values was substituted with LD. If any of the values were over the limit of quantitation (">LQ") in the data, these values were substituted with LQ.		

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Safety

Safety objectives of the study were to assess toxicity and side effects parameters at every visit, in particular prostatic specific antigen (PSA), hemoglobin and lipids as well as adverse events.

Corresponding endpoint is:

- Toxicity (adverse events) assessed according to the National Cancer Institute Common Toxicity Criteria version 4.0.
- Abnormal PSA (>2.5 ng/mL), abnormal HDL cholesterol (>40 mg/dL), abnormal LDL cholesterol (≤40 mg/dL).

Compliance

The objective is to compare the compliance in the three treatment arms.

The corresponding endpoints are:

- Treatment interruption with reasons.
- Premature permanent treatment discontinuation with reasons.

Quality of life

The objective is to compare the scores according to Male Questionnaires (International Index of Erectile Function, Aging Male Symptom Score, International Prostate Symptom Score).

The endpoints are the corresponding scores at baseline, at 3 months and at 6 months and their changes from baseline to 3 and 6 months.

To note, the implications of the quality of life questionnaires are the followings:

- Aging Male Symptom Score: <26 no significant symptoms consistent with a low testosterone level; 27-36 mild symptoms consistent with a low testosterone level; 37-49 moderate symptoms consistent with a low testosterone level; >50 severe symptoms consistent with a low testosterone level.
- Dimensions Erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction Score: 1-10 severe erectile dysfunction, 11-16 moderate dysfunction, 17-21 mild to moderate dysfunction, 22-25 mild dysfunction, 26-30 no dysfunction.
- International Prostate Symptom Score (used to define patient´s urinary symptoms): 0-7 mildly symptomatic, 8-19 moderately symptomatic, 20-35 severely symptomatic.
- To the separate patient's perceived quality of life question, is assigned a score of 0 (delighted) to 6 (terrible).

Statistical Methods:

Data Subsets

Modified Intent-to-treat set

All randomized patients who received at least one application of the study treatment were included in the modified intent-to-treat set. All patients from modified intent-to-treat set providing serum sample at baseline and at 3 months (or at end of treatment, if end of treatment was before 3 months) were included in the primary

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efficacy set. Patients were analyzed according to the randomized treatment arm.

Per-protocol set

All patients of the modified intent-to-treat set who completed three months of study treatment and provide estradiol samples at baseline and after three months of treatment were included in the per protocol set for primary efficacy analysis. In per protocol analysis subjects have been analyzed according to the actual study treatment received.

Safety set

All patients from the modified intent-to-treat set were included in the safety set; safety and compliance as well as quality of life analyses were performed based on actual treatment received.

Evaluable patients sets for secondary efficacy in terms of hormone values:

- The evaluable patients set for the secondary efficacy at 3 month is the primary efficacy set.
- All patients from the modified intent-to-treat set providing serum sample at baseline and at six months (or at end of treatment, if end of treatment was between 3 and 6 months) were included in the secondary efficacy set for 6 months.

Sample size determination

The following assumptions were made:

- The mean estradiol level at baseline is 25 pg/mL with the standard deviation of 8 pg/mL[1].
- After three months therapy the mean estradiol level will stay at 25 pg/mL in the tamoxifen only group, will decrease to 12.5 pg/mL (50% decrease) in the tamoxifen plus gonadotropin-releasing hormone analogue group and will decrease to 5 pg/mL (80% decrease) in the aromatase inhibitor plus gonadotropin-releasing hormone analogue group[1].
- The common standard deviation for the decrease in estradiol after three months therapy will be 16 pg/mL (conservatively estimated, based on the standard deviation of the estradiol level)[1].

1. Leder BZ, Rohrer JL, Rubin SD et al. Effects of Aromatase Inhibition in Elderly Men with Low or Borderline-Low Serum Testosterone Levels. J Clin Endo Metab 89(3):1174-80.

Then 14 patients per group are needed for the F-test to have 80% power to detect at the 5% significance level a difference in mean estradiol decrease between three therapy groups. The computation was made with the nQuery Advisor 6.0. Since it is possible that the estradiol level is not normally distributed and the non-parametric test (Kruskal-Wallis) must be used, the total sample size of 48 patients for the study was taken.

General principles

The overall significance level for the study is set to α=0.05, all statistical tests are 2-sided.

Continuous parameters have been summarized as mean, standard deviation, median, minimum and maximum, Q1 and Q3. Categorical variables have been summarized as number and (valid) percentage of subjects. Two-sided 95% confidence intervals have been presented where appropriate.

Analysis of demographic and baseline characteristics

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The patient and baseline characteristics have been presented descriptively for each study arm and overall; statistical tests have been performed to check for imbalance between treatment groups. The Pearson $\chi 2$-test (for categorical parameters), Kruskal-Wallis test (for continuous parameters) were used to assess the comparability of three randomized treatment arms.

Primary efficacy analysis

Primarily, the Kruskal-Wallis test (due to the failed test of normality) was used to compare the decrease of estradiol level after three months study treatment between study arms. The null hypothesis is that there is no difference in estradiol suppression between treatment arms, the alternative hypothesis that there is such difference. Since the primary test was statistically significant, then pairwise comparisons of tamoxifen plus gonadotropin-releasing hormone analogue, aromatase inhibitor plus gonadotropin-releasing hormone analogue versus tamoxifen alone arm was performed, using Wilcoxon-Mann-Whitney test. The general linear model was fitted for the primary endpoint estradiol decrease after 3 months adjusting for the following covariates: prior chemotherapy yes vs no as stratified, body-mass index (<30 kg/m^2 vs ≥ 30 kg/m^2) and age (continuous). The analysis in the subgroups according to previous chemotherapy was performed in the same way as the primary analysis.

Secondary efficacy analysis

Secondarily, the decrease of estradiol level after six months of treatment has been compared in the same way. The changes in other hormones (testosterone, dehydrotestosterone, sex hormone-binding globulin, follicle-stimulating hormone, luteinizing hormone, osteocalcin and free androgene index) levels after three and six months have been compared in the same way using non-parametric tests. The general linear model was fitted for the secondary endpoint estradiol decrease after six months adjusting for the same covariates as for the primary endpoint.

Since no neoadjuvant and only three metastatic patients (all in tamoxifen arm) were recruited into the study, no comparison of response between arms was possible.

Subgroup analysis

The subgroup analysis for the primary endpoint was performed for the primary efficacy set (as randomized), according to the previous chemotherapy (as stratified). In case of found differences between subgroups for the primary endpoint, the subgroup analysis was to be repeated for the other hormone endpoints, but this was not the case.

Safety analysis

The National Cancer Institute Common Toxicity Criteria version 4.0 and the corresponding grading system were used to grade adverse events for recording in the case report form. For all adverse events not classified by the National Cancer Institute Common Toxicity Criteria, a Coding Symbols for a Thesaurus of Adverse Reaction Terms grading classification (Food and Drug Administration 1989) was performed (severity as 1: mild, 2: moderate, 3: severe, 4: life-threatening, and 5: death). One adverse event could not be graded by the site; it was included in the analysis of "any grade" (grade 1-4) versus no and grade 3-4 versus low grade (as low grade since it was not reported as severe adverse event); but was not included in the analysis by grade (is presented as

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missing). Analysis of adverse events includes all laboratory data (e.g. observed toxicities). No separate analysis of laboratory data was planned, but may be performed in future. The proportions of patients experiencing any toxicity of National Cancer Institute Common Toxicity Criteria grade 1-4 and grade 3-4 were compared between treatment groups using Pearson $\chi 2$-test.

Compliance analysis

Descriptive statistics were given on the number of patients whose treatment had to be interrupted or permanently stopped. The reason for termination includes 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.

Quality of life analysis

Changes from baseline in each score were compared for the treatment groups after three months of treatment and after six months of treatment using the Kruskal-Wallis test. The categorized Aging Male Symptom Score, International Index of Erectile function and additional quality of life question for International Prostate Symptom Score were compared between arms at baseline, at three months and at six months with $\chi 2$ test.

SUMMARY

Between October 2012 and May 2017, 56 patients were randomized within 24 centers in Germany and 52 started treatment. One patient was randomized to receive Tamoxifen together with gonadotropin releasing hormone analogue, but was treated with Tamoxifen alone. The median age was 62 years (range 37-83 years). The median body mass index was 26.8 Kg/m^2. The majority of patients had a T2 (52.9%), N0 (52.0%), G2 (57.7%), HER2-negative (86.5%), breast cancer. Two patients had metastatic disease at diagnosis. Overall, 36.5% of the patients received prior chemotherapy for their breast cancer.

50 patients were fully evaluable and comprised the efficacy analysis set.

Efficacy Results:

Primary efficacy objective

Median (range) levels of estradiol in ng/L at baseline were 27.0 (5.0, 46.0) in arm A, 33.0 (14.0, 45.0) in arm B, 27.5 (17.0, 113.0) in arm C (p=0.281). After 3 months of treatment, median (range) levels of estradiol were 45.0 (19.0, 62.0) in arm A, 5.0 (5.0, 46.0) in arm B, 7.5 (5.0, 42.0) in arm C (p<0.001).

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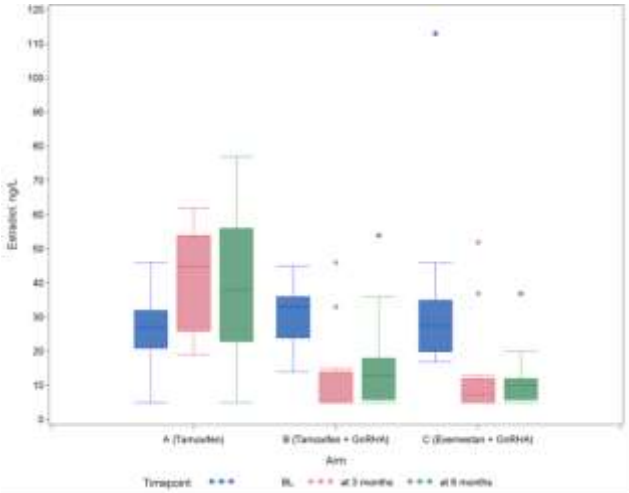
Figure 1: Estradiol at baseline, 3 months and 6 months, all evaluable patients, boxplot



The changes in estradiol level between baseline and month 3 were significantly different between treatment arms (median change (range): arm A 17.0 (-6.0, 29.0); arm B -23.0 (-40.0, 22.0); arm C -18.5 (-100.0, 21.0); p<0.001); pairwise comparisons of arm B vs A (p<0.001) and arm C vs A (p<0.001) were also significant. The changes in estradiol level between baseline and month 3 were significantly different between treatment arms when considering only patients who received (arm A 20.0 (13.0, 24.0); arm B -29.0 (-40.0, -14.0); arm C -18.0 (-100.0, -10.0); p=0.002) or not received (arm A 14.0 (-6.0, 29.0); am B 22.0 (-28.0, 22.0); arm C 21.0 (-41.0, -21.0) p=0.001) prior chemotherapy for their breast cancer (subgroup analysis). The multivariate analysis including treatment arm, BMI (<30 kg/m^2 vs ≥30 kg/m^2), prior chemotherapy (yes vs no) and age (continuous) confirmed the statistical significance of treatment arm (p<0.001).

Secondary efficacy objectives

Estradiol

After 6 months of treatment, median (range) levels of estradiol in ng/L were 38.0 (5.0, 77.0) in arm A, 13.0 (5.0, 54.0) in arm B, 10.0 (5.0, 37.0) in arm C (p<0.001). The changes in estradiol level between baseline and month 6 were significantly different between treatment arms (median change (range): arm A 12.0, (-23.0, 50.0); arm B -19.5 (-38.0, 30.0); arm C -17.0 (-102.0, 6.0); p<0.001); the multivariate analysis confirmed the statistical significance of treatment arm for estradiol change at 6 months (p<0.001).

Osteocalcine

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Median (range) levels of osteocalcine in µg/L at baseline were 19.9 (9.0, 36.1) in arm A, 16.7 (6.9, 39.4) in arm B, 14.4 (4.7, 24.3) in arm C (p=0.325). After 3 months of treatment, median (range) levels of osteocalcin were 16.0 (5.3, 88.0) in arm A, 14.9 (4.2, 23.2) in arm B, 18.8 (6.3, 42.6) in arm C (p=0.097). The changes in osteocalcine level were significantly different between treatment arms, between baseline and month 3 (median change, range: arm A -3.5 (-15.3, 67.2); arm B -2.8 (-16.2, 1.3); arm C -2.9 (-10.5, 19.6); p<0.001). After 6 months of treatment, median (range) levels of osteocalcine were 13.5 (2.6, 40.8) in arm A, 12.7 (6.0, 29.6) in arm B, 24.0 (12.8, 42.5) in arm C (p=0.002). The changes in osteocalcine level between baseline and month 6 were significantly different between treatment arms (median change, range: arm A -7.1 (-21.0, 24.8); arm B -4.0 (-11.1, 0.8); arm C 7.0 (-2.0, 25.7); p<0.001).

Testosterone

Median (range) levels of testosterone in µg/L at baseline were 3.7 (1.2, 7.1) in arm A, 3.9 (0.8, 10.7) in arm B, 4.0 (1.1, 15.0) in arm C (p=0.732). After 3 months of treatment, median (range) levels of testosterone were 6.2 (2.2, 11.4) in arm A, 0.1 (0.1, 6.1) in arm B, 0.3 (0.1, 15.0) in arm C (p<0.001). The changes in testosterone level were significantly different between treatment arms, between baseline and month 3 (median change (range): arm A 2.2 (-1.0, 4.7); arm B -3.8 (-10.6, 3.5); arm C -3.6 (-14.6, 7.1); p<0.001). After 6 months of treatment, median (range) levels of testosterone were 6.0 (0.2, 13.1) in arm A, 0.1 (0.1, 6.9) in arm B, 0.3 (0.1, 10.9) in arm C (p<0.001). The changes in testosterone level between baseline and month 6 were significantly different between treatment arms (median change (range): arm A 1.6 (-3.1, 8.3); arm B -3.7 (-10.6, 4.3); arm C -3.5 (-14.7, 1.0); p<0.001).

Dihydrotestosterone

Median (range) levels of dihydrotestosterone in ng/L at baseline were 282.0 (30.0, 818.0) in arm A, 245.0 (78.0, 759.0) in arm B, 321.5 (68.0, 1040.0) in arm C (p=0.145). After 3 months of treatment, median (range) levels of dihydrotestosterone were 361.0 (30.0, 886.0) in arm A, 32.0 (30.0, 450.0) in arm B, 30.0 (30.0, 1290.0) in arm C (p<0.001). The changes in dihydrotestosterone level were significantly different between treatment arms, between baseline and month 3 (median change (range): arm A 94.0 (-20.0, 417.0); arm B -188.0 (-719.0, 205.0); arm C -288.5 (-755.0, 277.0); p<0.001). After 6 months of treatment, median (range) levels of dihydrotestosterone were 471.0 (73.0, 1640.0) in arm A, 33.5 (30.0, 772.0) in arm B, 39.0 (30.0, 2090.0) in arm C (p<0.001). The changes in dihydrotestosterone level between baseline and month 6 were significantly different between treatment arms (median change (range): arm A 215.0 (35.0, 822.0); arm B -180.0 (-729.0, 527.0); arm C -225.0 (-762.0, 1050.0); p<0.001).

Sex hormone-binding globulin

Median (range) levels of sex hormone-binding globulin in nmol/L at baseline were 48.0 (17.0, 108.0) in arm A, 52.0 (26.0, 128.0) in arm B, 55.0 (16.0, 132.0) in arm C (p=0.592). After 3 months of treatment, median (range) levels of sex hormone-binding globulin were 56.0 (24.0, 102.0) in arm A, 58.0 (40.0, 200.0) in arm B, 48.0 (9.0, 133.0) in arm C (p=0.409). The changes in sex hormone-binding globulin level were significantly different between treatment arms, between baseline and month 3 (median change (range): arm A 5.0 (-36.0, 41.0); arm B

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17.0 (-18.0, 72.0); arm C -6.5 (-34.0, 23.0); p<0.001). After 6 months of treatment, median (range) levels of sex hormone-binding globulin were 55.0 (27.0, 111.0) in arm A, 54.5 (39.0, 174.0) in arm B, 40.0 (11.0, 118.0) in arm C (p=0.259). The changes in sex hormone-binding globulin level between baseline and month 6 were significantly different between treatment arms (median change (range): arm A 9.0 (-20.0, 50.0); arm B 13.0 (-13.0, 89.0); arm C -10.0 (-47.0, 5.0); p<0.001).

Free androgene index

Free androgene index was computed from testosterone and sex hormone-binding globulin. Median (range) levels of free androgene index at baseline were 25.0 (8.0, 58.0) in arm A, 25.0 (6.0, 44.0) in arm B, 25.5 (13.0, 62.0) in arm C (p=0.990). After 3 months of treatment, median (range) levels of free androgene index were 38.0 (8.0, 83.0) in arm A, 1.0 (1.0, 49.0) in arm B, 2.0 (1.0, 176.0) in arm C (p<0.001). The changes in free androgene index level were significantly different between treatment arms, between baseline and month 3 (median change (range): arm A 12.0 (-7.0, 35.0); arm B -24.0 (-43.0, 24.0); arm C -22.5 (-56.0, 128.0); p<0.001). After 6 months of treatment, median (range) levels of free androgene index were 32.0 (3.0, 71.0) in arm A, 1.0 (1.0, 53.0) in arm B, 2.0 (1.0, 98.0) in arm C (p<0.001). The changes in free androgene index level between baseline and month 6 were significantly different between treatment arms (median change (range): arm A 11.0 (-30.0, 36.0); arm B -24.0 (-43.0, 28.0); arm C -20.0 (-56.0, 50.0); p<0.001).

Follicle-stimulating hormone

Median (range) levels of follicle-stimulating hormone in IU/L at baseline were 15.6 (1.8, 30.4) in arm A, 9.7 (2.7, 60.3) in arm B, 9.5 (2.6, 36.4) in arm C (p=0.962). After 3 months of treatment, median (range) levels of follicle-stimulating hormone were 16.2 (2.0, 51.9) in arm A, 1.5 (0.5, 11.0) in arm B, 6.0 (3.7, 13.6) in arm C (p<0.001). The changes in follicle-stimulating hormone level were significantly different between treatment arms, between baseline and month 3 (median change (range): arm A 5.0 (0.2, 21.5); arm B -9.1 (-56.6, 7.2); arm C -4.2 (-28.6, 5.9); p<0.001). After 6 months of treatment, median (range) levels of follicle-stimulating hormone were 11.2 (1.6, 33.8) in arm A, 1.1 (0.3, 15.0) in arm B, 5.6 (3.7, 11.0) in arm C (p<0.001). The changes in follicle-stimulating hormone level between baseline and month 6 were significantly different between treatment arms (median change (range): arm A 0.6 (-11.0, 8.3); arm B -9.7 (-57.3, 12.3); arm C -3.3 (-28.7, 4.5); p=0.022).

Luteinizing hormone

Median (range) levels of luteinizing hormone in IU/L at baseline were 6.3 (1.8, 13.8) in arm A, 7.4 (1.6, 23.1) in arm B, 7.6 (3.3, 23.4) in arm C (p=0.673). After 3 months of treatment, median (range) levels of luteinizing hormone were 11.3 (3.3, 30.2) in arm A, 0.1 (0.1, 6.5) in arm B, 0.1 (0.1, 18.6) in arm C (p<0.001). The changes in luteinizing hormone level were significantly different between treatment arms, between baseline and month 3 (median change (range): arm A 4.1 (-0.7, 18.1); arm B -7.3 (-23.0, 4.9); arm C -7.5 (-23.3, 11.4); p<0.001). After 6 months of treatment, median (range) levels of luteinizing hormone were 8.4 (0.1, 33.9) in arm A, 0.1 (0.1, 11.0) in arm B, 0.1 (0.1, 17.7) in arm C (p<0.001). The changes in luteinizing hormone level between baseline and month 6 were significantly different between treatment arms (median change (range): arm A 2.5 (-13.7, 20.6); arm B -6.3 (-22.8, 8.8); arm C -7.0 (-18.8, 10.5); p<0.001).

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Treatment response in metastatic patients

Overall, 3 patients with metastatic disease were available for response analysis (all in Arm A): one patients experienced progressive disease after 3 months of treatment; the second one had a stable disease at month 3 and 6; the last one had a partial response after month 3 and 6.

Safety Results

Adverse events were analyzed in the safety population, overall and separately 3 and 6 months after starting study treatment. No significant differences were seen between arms in terms of any grade and any high grade adverse events neither when looking at the whole study duration (any grade: arm A 88.9%, arm B 100%, arm C 88.9%; p=0.382; high grade: arm A 16.7%, arm B 18.8%, arm C 27.8%; p=0.689), nor at 3 or 6 months after treatment start. Among the predefined adverse events the following were statistically significant different among the 3 arms: hot flashes any grade (arm A 11.1%, arm B 62.5%, arm C 66.7%; p=0.001), erectile dysfunction any grade (arm A 5.6%, arm B 50.0%, arm C 38.9%; p=0.013), libido decrease any grade (arm A 16.7%, arm B 56.3%, arm C 55.6%; p=0.025) and peripheral sensory neuropathy any grade (arm A 0.0%, arm B 0.0%, arm C 16.7%; p=0.049). After 3 months of treatment the following adverse events were statistically significant different between the three arms: hot flashes any grade (arm A 10.5%, arm B 53.3%, arm C 66.7%; p=0.002), myalgia any grade (arm A 0.0%, arm B 25.5%, arm C 5.6%; p=0.037) and erectile dysfunction any grade (arm A 5.3%, arm B 43.8%, arm C 27.8%; p=0.035). After six months of treatment the following significant differences were found between arms in term of adverse events: hot flashes any grade (arm A 5.9%, arm B 40.0%, arm C 47.1%; p=0.021), erectile dysfunction any grade (arm A 0.0%, arm B 46.7%, arm C 41.2%; p=0.005) and libido decrease any grade (arm A 5.9%, arm B 46.7%, arm C 41.2%; p=0.022). During the study a special safety focus was set on prostatic specific antigen, hemoglobin and lipids levels. No differences between arms was seen in anemia incidence; the incidence of total cholesterol increased was statistically significant different when looking at the whole study duration (any grade: arm A 16.7 %, arm B 18.8%, arm C 50.0%; p=0.049) and after six months of treatment (any grade: arm A 6.7%, arm B 15.4%, arm C 41.2%; p=0.050); the incidence of prostatic specific antigen increased was statistically significant different between arms only after 3 months of treatment (any grade: arm A 26.7%, arm B 0.0%, arm C 0.0%; p=0.014).

Only in one patient the study treatment (Tamoxifen + Gonadotropin releasing hormone analogue) was discontinued due to an adverse event (hyperglycemia) after about two months of therapy.

Overall, 5 patients experienced severe adverse events (9.6%) during the study and a total of 5 severe adverse events were reported. No significant difference was seen between arms (arm A 16.7%, arm B 6.3%, arm C 5.6%; p=0.454). No death was reported.

Compliance

One patient in each arm discontinued the study treatment: in arm A due to disease progression, in arm B due to adverse event and in arm C due to patient´s request. Overall, 3 patients in arm A (reason tablet forgotten/lost), 1

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in arm B (reason adverse event) and 2 in arm C (reasons: adverse event and other reason) interrupted the study treatment.

Quality of life

Aging Male Symptom Score (AMS)

The median (range) level obtained for the Aging Male Symptom Score at baseline was 28.0 (20.0, 57.0) in arm A, 33.0 (17.0, 47.0) in arm B, 26.5 (18.0, 50.0) in arm C; after 3 months: 30.0 (19.0, 63.0) in arm A, 40.0 (17.0, 57.0) in arm B, 38.6 (17.0, 60.0) in arm C; after 6 months: 31.0 (22.0, 43.6) in arm A, 38.0 (17.0, 55.0) in arm B, 43.5 (25.0, 56.3) in arm C.

The median change (range) in the Aging Male Symptom Score from baseline to month 3 was 2.0 (-30.0, 19.0) in arm A, 8.0 (-13.6, 21.0) in arm B, 11.2 (-6.4, 38.0) in arm C, whereas from baseline to month 6 was 2.0 (-32.9, 17.6) in arm A, 5.0 (-14.6, 21.0) in arm B, 11.5 (-5.0, 28.8) in arm C.

Figure 2: Aging Male Symptom Score at baseline, 3 months and 6 months, boxplot

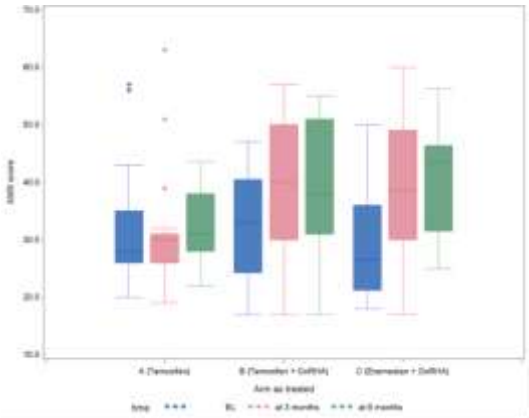

Table 1: Severity of complaints at baseline and after 3 months of treatment as defined by the Aging Male Symptom Score

Timepoint	Complaints	Arm A N(%) N=18	Arm B N(%) N=16	Arm C N(%) N=18	Overall N(%) N=52	p-value
Baseline	No complaints	7 (38.9)	5 (31.3)	9 (50.0)	21 (40.4)	0.194
	Minor complaints	7 (38.9)	4 (25.0)	6 (33.3)	17 (32.7)	
	Moderate complaints	2 (11.1)	7 (43.8)	2 (11.1)	11 (21.2)	

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	Strong complaints	2 (11.1)	0 (0.0)	1 (5.6)	3 (5.8)	
3 months	No complaints	6 (35.3)	1 (6.7)	4 (22.2)	11 (22.0)	0.051
	Minor complaints	8 (47.1)	5 (33.3)	3 (16.7)	16 (32.0)	
	Moderate complaints	1 (5.9)	4 (26.7)	8 (44.4)	13 (26.0)	
	Strong complaints	2 (11.8)	5 (33.3)	3 (16.7)	10 (20.0)	
	missing	1	1	0	2	
6 months	No complaints	4 (23.5)	2 (13.3)	2 (12.5)	8 (16.7)	0.283
	Minor complaints	7 (41.2)	5 (33.3)	3 (18.8)	15 (31.3)	
	Moderate complaints	6 (35.3)	4 (26.7)	8 (50.0)	18 (37.5)	
	Strong complaints	0 (0.0)	4 (26.7)	3 (18.8)	7 (14.6)	
	missing	0	0	1	1	

Dimensions Erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction Score (IIEF-15)

The median (range) level obtained for the Dimensions Erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction Score at baseline was 34.5 (5.0, 67.0) in arm A, 38.7 (5.0, 71.0) in arm B, 32.0 (5.0, 67.0) in arm C; after 3 months: 38.0 (5.0, 64.0) in arm A, 11.0 (5.0, 63.0) in arm B, 13.0 (5.0, 55.0) in arm C; after 6 months: 35.0 (6.0, 60.0) in arm A, 9.0 (5.0, 41.3) in arm B, 10.0 (5.0, 47.0) in arm C.

The median change (range) in the Dimensions Erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction Score from baseline to month 3 was 0.0 (-24.0, 39.0) in arm A, -24.0 (-63.0, 22.6) in arm B, 11.9 (-52.0, 31.0) in arm C, whereas from baseline to month 6 was 2.2 (-10.0, 16.8) in arm A, -26.0 (-63.0, 0.0) in arm B, -17.0 (-61.0, 31.0) in arm C.

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Figure 3: Dimensions Erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction Score at baseline, 3 months and 6 months, boxplot.

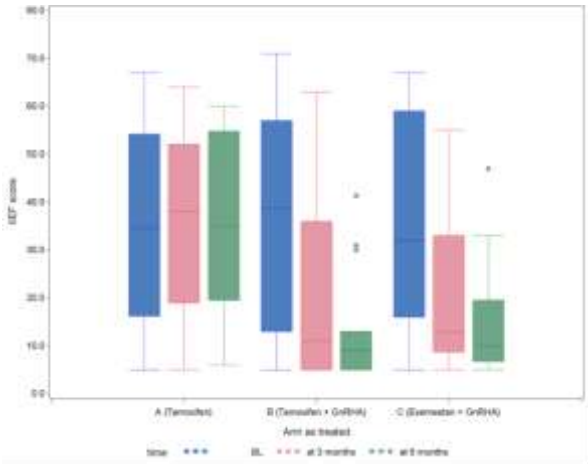

Table 2: potential signs of erectile dysfunction at baseline, after 3 and 6 months as defined by the Dimensions Erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction Score

Timepoint	Signs of erectile dysfunction	Arm A N(%) N=18	Arm B N(%) N=16	Arm C N(%) N=18	Overall N(%) N=52	p-value
Baseline	Potential signs	5 (27.8)	6 (37.5)	7 (38.9)	18 (34.6)	0.750
	No signs	13 (72.2)	10 (62.5)	11 (61.1)	34 (65.4)	
3 months	Potential signs	5 (29.4)	11 (73.3)	11 (61.1)	27 (54.0)	0.034
	No signs	12 (70.6)	4 (26.7)	7 (38.9)	23 (46.0)	
	missing	1	1	0	2	
6 months	Potential signs	4 (25.0)	12 (80.0)	13 (81.3)	29 (61.7)	<.001
	No signs	12 (75.0)	3 (20.0)	3 (18.8)	18 (38.3)	
	missing	1	0	1	2	

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International Prostate Symptom Score (IPSS)

The median (range) level obtained for the International Prostate Symptom Score at baseline was 5.5 (1.0, 16.0) in arm A, 5.0 (0.0, 26.0) in arm B, 4.5 (2.0, 20.0) in arm C; after 3 months: 8.0 (2.0, 15.0) in arm A, 7.0 (0.0, 21.0) in arm B, 6.0 (0.0, 18.0) in arm C; after 6 months: 7.5 (2.0, 17.0) in arm A, 11.0 (0.0, 26.0) in arm B, 5.5 (1.0, 27.0) in arm C. The median change (range) in the International Prostate Symptom Score from baseline to month 3 was 1.0 (-2.0, 6.0) in arm A, 1.0 (-8.0, 10.0) in arm B, 0.0 (-16.0, 13.0) in arm C, whereas from baseline to month 6 was 1.5 (-4.0, 7.0) in arm A, 2.0 (-3.0, 16.0) in arm B, 1.3 (-6.0, 17.0) in arm C.

Figure 4: International Prostate Symptom Score at baseline, 3 months and 6 months, boxplot.

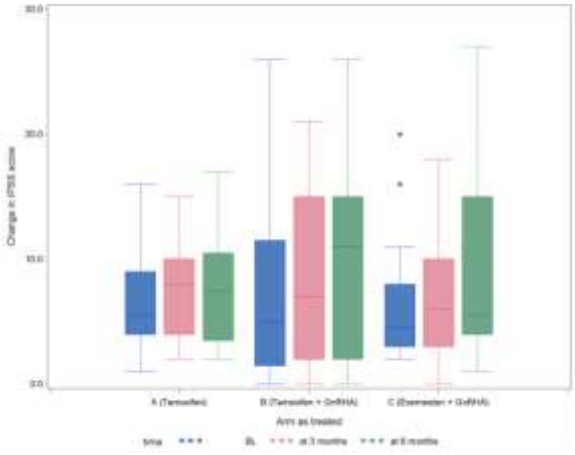

Table 3: Definition of quality of life due to urinary symptoms at baseline, after 3 and 6 months according to the International Prostate Symptom Score

Timepoint	Quality of life	Arm A N(%) N=18	Arm B N(%) N=16	Arm C N(%) N=18	Overall N(%) N=52	p-value
Baseline	Delighted (0)	2 (11.8)	3 (18.8)	5 (27.8)	10 (19.6)	0.340
	Pleased (1)	8 (47.1)	7 (43.8)	7 (38.9)	22 (43.1)	
	Mostly Satisfied (2)	7 (41.2)	3 (18.8)	3 (16.7)	13 (25.5)	
	Mixed (3)	0 (0.0)	3 (18.8)	3 (16.7)	6 (11.8)	
	Worst (4-6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Missing	1	0	0	1	
3 months	Delighted (0)	2 (11.8)	4 (28.6)	3 (17.6)	9 (18.8)	0.548
	Pleased (1)	6 (35.3)	5 (35.7)	6 (35.3)	17 (35.4)	
	Mostly Satisfied (2)	6 (35.3)	2 (14.3)	4 (23.5)	12 (25.0)	

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	Mixed (3)	3 (17.6)	2 (14.3)	2 (11.8)	7 (14.6)	
	Worst (4-6)	0 (0.0)	1 (7.1)	2 (11.8)	3 (6.3)	
	Missing	1	2	1	4	
6 months	Delighted (0)	3 (18.8)	3 (20.0)	3 (18.8)	9 (19.1)	0.737
	Pleased (1)	6 (37.5)	4 (26.7)	3 (18.8)	13 (27.7)	
	Mostly Satisfied (2)	4 (25.0)	3 (20.0)	4 (25.0)	11 (23.4)	
	Mixed (3)	2 (12.5)	4 (26.7)	2 (12.5)	8 (17.0)	
	Worst (4-6)	1 (6.3)	1 (6.7)	4 (25.0)	6 (12.8)	
	Missing	1	0	1	2	

CONCLUSIONS

The MALE is the first prospectively randomized Phase II study in male breast cancer. It investigates the effect of antihormonal therapy on predefined endocrine parameters and PRO after 3 and 6 months of therapy. Patients received either Tamoxifen, or the combination of Tamoxifen plus an LHRH agonist or Exemestane plus an LHRH agonist. Overall, the results reflect the expected changes of the hormonal parameters. The combination of gonadotropin releasing hormone analogue and tamoxifen (arm B) or LHRH and exemestane (arm C) led to a comparable reduction of estradiol, follicle-stimulating hormone and luteinizing hormone. The decrease of luteinizing hormone and of follicle-stimulating hormone consequently lead to a decrease in the aromatization of androgen to estradiol. The three different treatment strategies were well tolerated with no new safety concerns. The side effects of tamoxifen on the patients´ erectile function and quality of life were moderate, whereas the combination of tamoxifen or aromatase inhibitors with gonadotropin releasing hormone influenced the well-being and the erectile function in men deeply compared to baseline. These results will inform the physicians and patients when the decisions has to be made which endocrine therapy to use as part of the breast cancer treatment.

Date of the Report:
June 7th, 2019

Annex 1 - Protocol Amendments

There was one protocol amendment with the following main changes:

- Patients with DCIS will not be enrolled due to potential overtherapy.
- Extension of staging and lab value period before randomization.
- Adaption of PSA, ASAT, ALAT and bilirubin values.