



Clinical trial results: GENOTYPE AND PHENOTYPE GUIDED SUPPLEMENTATION OF TAMOXIFEN STANDARD THERAPY WITH ENDOXIFEN IN BREAST CANCER PATIENTS.

Summary

EudraCT number	2016-000418-31
Trial protocol	DE
Global end of trial date	03 May 2021

Results information

Result version number	v1 (current)
This version publication date	04 December 2025
First version publication date	04 December 2025
Summary attachment (see zip file)	Clinical Study Report (TAMENDOX_CSR_Vs 1.0_24-1-2025.pdf)

Trial information

Trial identification

Sponsor protocol code	IKP275
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03931928
WHO universal trial number (UTN)	U1111-1237-9906
Other trial identifiers	GBG Forschungs GmbH: GBG 91

Notes:

Sponsors

Sponsor organisation name	Robert Bosch Gesellschaft für medizinische Forschung mbH
Sponsor organisation address	Auerbachstr. 112, Stuttgart, Germany, 70376
Public contact	Sponsor, Robert Bosch Gesellschaft für medizinische Forschung mbH, 49 7118101 3700, matthias.schwab@ikp-stuttgart.de
Scientific contact	Sponsor, Robert Bosch Gesellschaft für medizinische Forschung mbH, +49 071181013700, matthias.schwab@ikp-stuttgart.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2021
Global end of trial reached?	Yes
Global end of trial date	03 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To increase (Z)-endoxifen steady state concentrations in patients with compromised CYP2D6 to levels observed in patients with full CYP2D6 activity. The target concentration is >32 nM.

Protection of trial subjects:

The clinical study was conducted in accordance with the Declaration of Helsinki (Somerset West, 1996), lastly amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) – Guideline for Good Clinical Practice E6(R2), and the respective Commission Directives in the European Community, as well as the German Medicinal Products Act and the German GCP Ordinance, and other applicable national German laws and regulations.

Prior to the start of the study, the favourable opinion of the Competent Ethics Committee (EC) (25 March 2019) and the approval of the Competent Authority (CA) (01 April 2019) were obtained. The clinical study was also submitted to the local EC of each study centre for review.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 338
Worldwide total number of subjects	338
EEA total number of subjects	338

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	314
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients who were receiving Tamoxifen therapy (20 mg/day) for at least three months and presumably matched the inclusion and exclusion criteria were approached and informed on the scope of the study.

Pre-assignment

Screening details:

Main Inclusion Criteria: Pre- and postmenopausal female patients with DCIS or stage I, IIA, IIB or IIIA invasive breast cancer who have received at least three months standard tamoxifen treatment before baseline visit

Main Exclusion Criteria: Locally advanced (Stage IIIB or IIIC) or metastatic (Stage IV) breast cancer at time of surgery, ongoing c

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Patients were randomly assigned to one of the three groups: Group 1 was the control group, received placebo; group 2: (Z)-endoxifen supplementation according to CYP2D6 genotype; group 3: (Z)-endoxifen supplementation according to basal (Z)-endoxifen plasma concentration in a 1:1:1 ratio. A permuted block design with random blocks was applied and the allocation sequence was generated using a computerized algorithm. The resulting randomization list was implemented in MedCODES®.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control group

Arm description:

Patients received placebo independent of CYP2D6 genotype

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Enteric-coated tablets containing 0 mg (Z)-endoxifen (Placebo)

Arm title	Genotype group
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Arm description:

Patients received (Z)-endoxifen dosed according to CYP2D6 "genotype" (i.e. genotype predicted IM or PM activity) or placebo (genotype predicted EM /UM).

Arm type	Experimental
Investigational medicinal product name	(Z)-endoxifen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet 1.5 mg per day or one tablet 3 mg per day or placebo depending on genotype

Arm title	Phenotype group
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Arm description:

Patients received (Z)-endoxifen dosed according to (Z)-endoxifen steady state plasma concentrations (phenotype) at screening (i.e. ≤ 15 nM or > 15 and ≤ 25 nM) under tamoxifen treatment with 20 mg/day or placebo (> 25 nM).

Arm type	Experimental
Investigational medicinal product name	(Z)-endoxifen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet 1.5 mg per day or one tablet 3 mg per day or placebo depending on phenotype

Number of subjects in period 1^[1]	Control group	Genotype group	Phenotype group
Started	83	81	82
Completed	79	78	78
Not completed	4	3	4
Physician decision	1	-	1
Patient's decision	3	2	2
COVID-19 infection	-	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Recruitment was interrupted from March to August 2020 due to COVID-19, and patient numbers were lower than expected. Thus, amendment 1 (26.06.2020) introduced an interim analysis with a corresponding SAP (29.12.2020). The interim results met the primary endpoint, so the study was terminated with 235 analyzed patients, within the sample range for stage 2 of the revised SAP (29.12.2020). Reaching the initially planned number of patients was therefore unnecessary.

Baseline characteristics

Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	246	246	
Age categorical			
18 -76 years			
Units: Subjects			
18 - 76 years	246	246	
Gender categorical			
Units: Subjects			
Female	246	246	

Subject analysis sets

Subject analysis set title	Genotype versus control
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Genotype group was compared with the control group

Subject analysis set title	Phenotype versus control
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Phenotype group was compared with the control group

Reporting group values	Genotype versus control	Phenotype versus control	
Number of subjects	157	157	
Age categorical			
18 -76 years			
Units: Subjects			
18 - 76 years	157	157	
Gender categorical			
Units: Subjects			
Female	157	157	

End points

End points reporting groups

Reporting group title	Control group
Reporting group description: Patients received placebo independent of CYP2D6 genotype	
Reporting group title	Genotype group
Reporting group description: Patients received (Z)-endoxifen dosed according to CYP2D6 "genotype" (i.e. genotype predicted IM or PM activity) or placebo (genotype predicted EM /UM).	
Reporting group title	Phenotype group
Reporting group description: Patients received (Z)-endoxifen dosed according to (Z)-endoxifen steady state plasma concentrations (phenotype) at screening (i.e. ≤ 15 nM or > 15 and ≤ 25 nM) under tamoxifen treatment with 20 mg/day or placebo (> 25 nM).	
Subject analysis set title	Genotype versus control
Subject analysis set type	Intention-to-treat
Subject analysis set description: Genotype group was compared with the control group	
Subject analysis set title	Phenotype versus control
Subject analysis set type	Intention-to-treat
Subject analysis set description: Phenotype group was compared with the control group	

Primary: proportion of patients in the control group that reaches steady state (Z)-endoxifen plasma concentration of > 32 nM

End point title	proportion of patients in the control group that reaches steady state (Z)-endoxifen plasma concentration of > 32 nM
End point description: The primary endpoint is reached if in one or both intervention groups, the proportion of patients with steady state (Z)-endoxifen plasma concentration > 32 nM is greater or equal to the proportion of patients in the control group that reaches steady state (Z)-endoxifen plasma concentration of > 32 nM	
End point type	Primary
End point timeframe: 6 weeks	

End point values	Control group	Genotype group	Phenotype group	Genotype versus control
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	79	78	78	157
Units: 1	79	78	78	157

End point values	Phenotype versus control			
Subject group type	Subject analysis set			
Number of subjects analysed	157			
Units: 1	157			

Statistical analyses

Statistical analysis title	Efficacy Analyses
Statistical analysis description: Comparison of the proportion of patients with steady state (Z)-endoxifen plasma levels above 32 nM endoxifen following (Z)-endoxifen supplementation after 6 weeks.	
Comparison groups	Control group v Genotype group v Phenotype group
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	≤ 0.05
Method	Mantel-Haenszel

Notes:

[1] - The proportion of patients with steady state (Z)-endoxifen plasma levels above 32 nM endoxifen following (Z)-endoxifen supplementation after 6 weeks were compared to the control group (Group 1) and statistically assessed by means of two Mantel-Haenszel χ^2 -tests (Group 2 vs. control and Group 3 vs. control) to examine the null hypothesis of equal proportions in the supplementation groups and the control group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were monitored from the date of the first administration of study medication (6 weeks) and 4 weeks of follow-up (visits 1–4).

Adverse event reporting additional description:

All AEs in patients who received 3 mg (Z)-endoxifen, 1.5 mg (Z)-endoxifen, or placebo are listed. AEs were monitored from the date of the first administration of study medication and 4 weeks of follow-up (visits 1–4). In case the same AE was observed several times, it was counted only once with the greatest severity monitored. For the individual or

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Control group
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Reporting group description:

Placebo group

Reporting group title	Genotype group
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Reporting group description: -

Reporting group title	Phenotype group
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Reporting group description: -

Serious adverse events	Control group	Genotype group	Phenotype group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 79 (0.00%)	0 / 78 (0.00%)	0 / 78 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Control group	Genotype group	Phenotype group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 79 (84.81%)	63 / 78 (80.77%)	65 / 78 (83.33%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 79 (5.06%)	9 / 78 (11.54%)	3 / 78 (3.85%)
occurrences (all)	16	16	16
Aspartate aminotransferase increased			

subjects affected / exposed	6 / 79 (7.59%)	7 / 78 (8.97%)	4 / 78 (5.13%)
occurrences (all)	17	17	17
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 79 (12.66%)	8 / 78 (10.26%)	4 / 78 (5.13%)
occurrences (all)	22	22	22
Blood creatine increased			
subjects affected / exposed	5 / 79 (6.33%)	6 / 78 (7.69%)	4 / 78 (5.13%)
occurrences (all)	15	15	15
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 79 (11.39%)	11 / 78 (14.10%)	6 / 78 (7.69%)
occurrences (all)	26	26	26
Vascular disorders			
Hot flush			
subjects affected / exposed	23 / 79 (29.11%)	25 / 78 (32.05%)	26 / 78 (33.33%)
occurrences (all)	74	74	74
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 79 (6.33%)	7 / 78 (8.97%)	2 / 78 (2.56%)
occurrences (all)	14	14	14
Headache			
subjects affected / exposed	21 / 79 (26.58%)	19 / 78 (24.36%)	19 / 78 (24.36%)
occurrences (all)	59	59	59
Paraesthesia			
subjects affected / exposed	7 / 79 (8.86%)	1 / 78 (1.28%)	3 / 78 (3.85%)
occurrences (all)	11	11	11
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 79 (24.05%)	10 / 78 (12.82%)	14 / 78 (17.95%)
occurrences (all)	43	43	43
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 79 (2.53%)	1 / 78 (1.28%)	5 / 78 (6.41%)
occurrences (all)	8	8	8
Gastrointestinal disorders			
Constipation			

subjects affected / exposed occurrences (all)	5 / 79 (6.33%) 11	1 / 78 (1.28%) 11	5 / 78 (6.41%) 11
Nausea subjects affected / exposed occurrences (all)	8 / 79 (10.13%) 14	2 / 78 (2.56%) 14	4 / 78 (5.13%) 14
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 4	4 / 78 (5.13%) 4	0 / 78 (0.00%) 4
Vaginal discharge subjects affected / exposed occurrences (all)	8 / 79 (10.13%) 18	7 / 78 (8.97%) 18	3 / 78 (3.85%) 18
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	5 / 79 (6.33%) 12	3 / 78 (3.85%) 12	4 / 78 (5.13%) 12
Dry skin subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 8	4 / 78 (5.13%) 8	2 / 78 (2.56%) 8
Rash subjects affected / exposed occurrences (all)	4 / 79 (5.06%) 8	2 / 78 (2.56%) 8	2 / 78 (2.56%) 8
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	7 / 79 (8.86%) 13	2 / 78 (2.56%) 13	4 / 78 (5.13%) 13
Sleep disorder subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 9	3 / 78 (3.85%) 9	4 / 78 (5.13%) 9
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	6 / 79 (7.59%) 18	8 / 78 (10.26%) 18	4 / 78 (5.13%) 18
Bone pain subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 5	4 / 78 (5.13%) 5	1 / 78 (1.28%) 5

Muscle spasms subjects affected / exposed occurrences (all)	10 / 79 (12.66%) 25	8 / 78 (10.26%) 25	7 / 78 (8.97%) 25
Myalgia subjects affected / exposed occurrences (all)	8 / 79 (10.13%) 17	4 / 78 (5.13%) 17	5 / 78 (6.41%) 17
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 11	2 / 78 (2.56%) 11	6 / 78 (7.69%) 11
Metabolism and nutrition disorders Fluid retention subjects affected / exposed occurrences (all)	6 / 79 (7.59%) 13	2 / 78 (2.56%) 13	5 / 78 (6.41%) 13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2020	Due to the COVID-19 pandemic, the patient recruitment had to be stopped in March 2020. In the substantial protocol amendment no. 1, dated 26-Jun-2020, an interim analysis was implemented and recruitment was restarted in August 2020. A hierarchical design was chosen to reduce the total number of patients necessary.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 March 2020	Due to the COVID-19 pandemic, patient recruitment had to be stopped in March 2020. In August 2020, a substantial amendment was prepared to resume the study (Amendment No. 1 (substantial), Version 1.0, dated 26 June 2020).	24 August 2020

Notes:

Limitations and caveats

None reported